

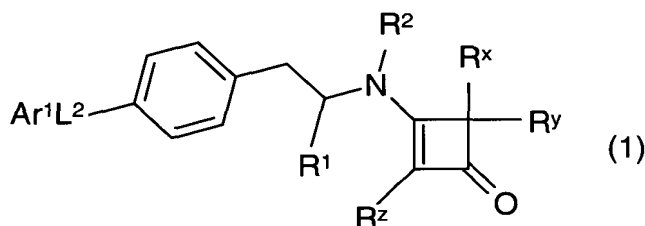
PROCESS FOR THE PREPARATION OF PHENYLALANINE ENAMIDE DERIVATIVES

5 The present invention relates to processes and intermediates for the synthesis of a class of phenylalanine enamide derivatives, the final products being useful as $\alpha 4$ integrin inhibitors.

The role of $\alpha 4$ integrin inhibitors, such as $\alpha 4\beta 7$ and/or $\alpha 4\beta 1$ inhibitors, for use in medicine is discussed, for example, in International Patent Application
10 Number WO 02/069393.

We have now developed a process for the production of a class of $\alpha 4$ integrin inhibitors, as defined hereinafter, which is particularly amenable for the large scale synthesis of the compounds. The process is simple to operate and
15 advantageously limits the need to use protecting groups.

Thus according to one aspect of the invention we provide a process for the preparation of phenylalanine enamide derivatives of the general formula (1):



20 wherein:

Ar¹ is an optionally substituted aromatic or heteroaromatic group;

L² is a linker group selected from -N(R⁴)- [where R⁴ is a hydrogen atom or an optionally substituted straight or branched C₁₋₆alkyl group], -CON(R⁴)-, or -S(O)₂N(R⁴)-;

25 R¹ is a carboxylic acid (-CO₂H) or a derivative or biostere thereof;

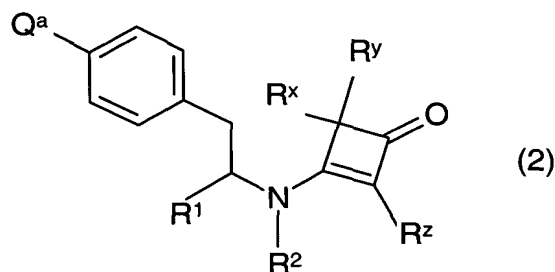
R² is a hydrogen atom or a C₁₋₆alkyl group;

R^x, R^y and R^z which may be the same or different is each an atom or group -L¹(Alk¹)_n(R³)_v in which L¹ is a covalent bond or a linker atom or group, Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain, R³ is a hydrogen or

halogen atom or group selected from $-OR^{3a}$ [where R^{3a} is a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group or C_{3-8} cycloalkyl group], $-SR^{3a}$, $-CN$ or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group, n is zero or the integer 1 and v is the integer 1, 2 or 3 provided that when n is zero and L^1 is a covalent bond v is the integer 1; or R^z is an atom or group as previously defined and R^x and R^y are joined together to form an optionally substituted spiro linked cycloaliphatic or heterocycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof;

which comprises reacting a compound of formula (2):



wherein:

Q^a is a group $-N(R^4)H$;

and the salts, solvates, hydrates and N-oxides thereof;

with a compound Ar^1W wherein W is a group selected from X^1 (wherein X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulfonyloxy group such as an alkylsulfonyloxy, e.g. trifluoro-methylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group), $-COX^2$ (wherein X^2 is a halogen atom such as a chlorine atom or a $-OH$ group) or $-SO_2X^3$ (in which X^3 is a halogen atom such as chlorine).

It will be appreciated that compounds of formulae (1), (2) or Ar^1W may have one or more chiral centres, and exist as enantiomers or diastereomers. The process is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formulae (1), (2) or Ar^1W and the formulae hereinafter are intended to represent all individual isomers and

mixtures thereof, unless stated or shown otherwise. In addition, compounds of formulae (1), (2) or Ar¹W may exist as tautomers, for example keto (CH₂C=O)-enol (CH=CHOH) tautomers. Formulae (1), (2) or Ar¹W and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

In the compounds described herein optionally substituted aromatic groups which may be represented by the group Ar¹ include for example optionally substituted monocyclic or bicyclic fused ring C₆₋₁₂aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups which may be represented by the group Ar¹ include for example optionally substituted C₁₋₉heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, e.g. 2,6-naphthyridinyl, or 2,7-naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl,

pyrido[4,3-b]pyridyl, quinoliny, isoquinoliny, tetrazolyl, 5,6,7,8-tetrahydroquinoliny, 5,6,7,8-tetrahydro-isoquinoliny, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

- 5 Each aromatic or heteroaromatic group represented by the group Ar¹ may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group -L³(Alk²)_tL⁴(R⁵)_u in which L³ and L⁴, which may be the same or
- 10 different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk² is an optionally substituted aliphatic or heteroaliphatic chain and R⁵ is a hydrogen or halogen atom or a group selected from optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl, -OR⁶ [where R⁶ is a hydrogen atom, an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl
- 15 group], -SR⁶, -NR⁶R⁷ [where R⁷ is as just defined for R⁶ and may be the same or different], -NO₂, -CN, -CO₂R⁶, -SO₃H, -SOR⁶, -SO₂R⁶, -SO₃R⁶, -OCO₂R⁶, -CONR⁶R⁷, -OCONR⁶R⁷, -CSNR⁶R⁷, -COR⁶, -OCOR⁶, -N(R⁶)COR⁷, -N(R⁶)CSR⁷, -SO₂N(R⁶)(R⁷), -N(R⁶)SO₂R⁷, N(R⁶)CON(R⁷)(R⁸) [where R⁸ is a hydrogen atom, an optionally substituted C₁₋₆alkyl or C₃₋
- 20 8cycloalkyl group], -N(R⁶)CSN(R⁷)(R⁸) or -N(R⁶)SO₂N(R⁷)(R⁸), provided that when t is zero and each of L³ and L⁴ is a covalent bond then u is the integer 1 and R⁵ is other than a hydrogen atom.

- When L³ and/or L⁴ is present in these substituents as a linker atom or group it
- 25 may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R⁸)- [where R⁸ is a hydrogen atom or an optionally substituted straight or branched C₁₋₆alkyl group], -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, -N(R⁸)O-, -ON(R⁸)-, -
- 30 N(R⁸)N(R⁸)-, -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸)-, or -N(R⁸)SO₂N(R⁸)- groups.

Where the linker group contains two R⁸ substituents, these may be the same or different.

When R^{3a}, R⁴, R⁵, R⁶, R⁷ and/or R⁸ is present as a C₁₋₆alkyl group it may be
5 a straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl, ethyl or i-propyl group. C₃₋₈cycloalkyl groups represented by R^{3a}, R⁵, R⁶, R⁷ and/or R⁸ include C₃₋₆cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be
10 present on such alkyl or cycloalkyl groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy e.g. methoxy or ethoxy groups.

When the groups R⁶ and R⁷ or R⁷ and R⁸ are both C₁₋₆alkyl groups these
15 groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or -N(R⁶)-. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

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When Alk² is present as an optionally substituted aliphatic or heteroaliphatic chain it may be any optionally substituted aliphatic or heteroaliphatic chain as described hereinafter for Alk¹.

25 Halogen atoms represented by R⁵ in the optional Ar¹ substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by -L³(Alk²)_tL⁴(R⁵)_u when present
in Ar¹ groups in compounds of formulae (1) or (iii) include atoms or groups -
30 L³Alk²L⁴R⁵, -L³Alk²R⁵, -L³R⁵, -R⁵ and -Alk²R⁵ wherein L³, Alk², L⁴ and R⁵ are as defined above. Particular examples of such substituents include -

$L^3CH_2L^4R^5$, $-L^3CH(CH_3)L^4R^5$, $-L^3(CH_2)_2L^4R^5$, $-L^3CH_2R^5$, $-L^3CH(CH_3)R^5$, $-L^3(CH_2)_2R^5$, $-CH_2R^5$, $-CH(CH_3)R^5$, $-(CH_2)_2R^5$ and $-R^5$ groups.

Thus Ar^1 in compounds of formulae (1) or Ar^1W may be optionally substituted
 5 for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, carboxy C_{1-6} alkyl, e.g. carboxyethyl, C_{1-6} alkylthio e.g.
 10 methylthio or ethylthio, carboxy C_{1-6} alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6} alkoxy, e.g. methoxy or ethoxy, hydroxy C_{1-6} alkoxy, e.g. 2-hydroxyethoxy, halo C_{1-6} alkyl, e.g. $-CF_3$, $-CHF_2$, $-CH_2F$, halo C_{1-6} alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6} alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), amino C_{1-6} alkyl, e.g. aminomethyl
 15 or aminoethyl, C_{1-6} dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6} alkylamino C_{1-6} alkyl, e.g. ethyl-aminoethyl, C_{1-6} dialkylamino C_{1-6} alkyl, e.g. diethylaminoethyl, amino C_{1-6} alkoxy, e.g. aminoethoxy, C_{1-6} alkylamino C_{1-6} alkoxy, e.g. methylamino-ethoxy, C_{1-6} dialkylamino C_{1-6} alkoxy, e.g. dimethylaminoethoxy, diethyl-aminoethoxy, diisopropylaminoethoxy or
 20 dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl ($-OH$), formyl [$HC(O)-$], carboxyl ($-CO_2H$), $-CO_2R^6$ e.g. $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, C_{1-6} alkanoyl e.g. acetyl, thiol ($-SH$), thio C_{1-6} alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3R^6$, C_{1-6} alkylsulphinyl, e.g. methylsulphinyl, C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl,
 25 e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6} alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino C_{1-6} alkyl-
 30 aminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6} alkylamino C_{1-6} alkylaminocarbonyl, e.g. ethylaminoethylaminocarbonyl, C_{1-6} dialkylamino C_{1-6}

₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, amino-
 carbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonyl-
 amino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g.
 dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆
 5 ₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethyl-amino,
 aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g.
 methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆
₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or
 diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkyl-amino,
 10 e.g. ethylaminothiocabonylmethylamino, C₁₋₆alkylsulphonylamino, e.g.
 methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkyl-sulphonylamino,
 e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino
 (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g.
 methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkyl-
 15 aminosulphonylamino, e.g. dimethylaminosulphonylamino or diethyl-
 aminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆
 alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoyl-amino,
 e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g.
 acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamido-
 20 ethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino,
 ethoxycarbonylamino or t-butoxycarbonylamino groups.

When the group R² is present in compounds of formulae (1) or (2) as a C₁₋₆
 alkyl group it may be for example a straight or branched C₁₋₆alkyl group e.g.
 25 a C₁₋₃alkyl group such as a methyl or ethyl group.

When the group R¹ in compounds of formulae (1) or (2) is present as a
 derivative of a carboxylic acid it may be for example an acyclic or cyclic
 carboxylic acid ester or an amide. Particular acyclic esters and amides include
 30 -CO₂Alk⁷ and -CONR⁶R⁷ groups as defined herein. When R¹ is a biostere of
 a carboxylic acid it may be for example a tetrazole or other acid such as

phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

Esterified carboxyl groups represented by the group $-\text{CO}_2\text{Alk}^7$ include groups

5 wherein Alk^7 is a straight or branched optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl or neopentyl group; an optionally substituted C_{2-8} alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8} alkynyl group such as a ethynyl, propynyl e.g. 2-

10 propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8} cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8} heterocycloalkyl group such as a tetrahydrofuranyl e.g. tetrahydrofuran-3-yl, pyrrolidinyl e.g. 1-methylpyrrolidinyl such as 1-methylpyrrolidin-3-yl, piperidinyl e.g. 1-

15 methylpiperidinyl such as 1-methylpiperidin-4-yl, tetrahydropyranyl e.g. tetrahydropyran-4-yl or 2-oxo-[1,3]dioxol-4-yl e.g. 5-methyl-2-oxo-[1,3]dioxol-4-yl group; an optionally substituted C_{3-8} cycloalkyl C_{1-8} alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8} heterocycloalkyl C_{1-8} alkyl group such as a morpholinyl-N-

20 ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6} alkyloxy C_{1-6} alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted hydroxy C_{1-6} alkyl group such as a hydroxyethyl e.g. 2-hydroxyethyl or hydroxypropyl e.g. 2-hydroxypropyl,

25 3-hydroxypropyl or 2,3-dihydroxypropyl group; an optionally substituted C_{1-6} alkylthio C_{1-6} alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6} alkylsulfinyl C_{1-6} alkyl group such as an methylsulfinylethyl group; an optionally substituted C_{1-6} alkylsulfonyl C_{1-6} alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8} cycloalkyloxy C_{1-6} alkyl group such as a cyclohexyloxymethyl group; an optionally substituted

30 C_{3-8} cycloalkylthio C_{1-6} alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8} cycloalkylsulfinyl C_{1-6} alkyl group such as a

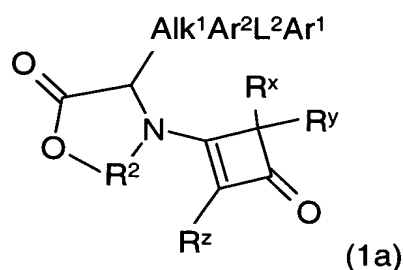
cyclopentyl-sulfinylmethyl group; an optionally substituted C₃₋₈cycloalkylsulfonylC₁₋₆alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkyl group such as isobutoxy-carbonylpropyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkyl group such as an ethyloxycarbonyloxymethyl or isopropoxycarbonyloxyethyl e.g. 1-(isopropoxycarbonyloxy)ethyl or 2-(isopropoxycarbonyloxy)ethyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C₃₋₈cycloalkyloxycarbonyloxyC₁₋₆alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C₁₋₈alkylaminoC₁₋₈alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C₆₋₁₂aryl-N-C₁₋₆alkylaminoC₁₋₆alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C₁₋₈alkyl-carbamoylC₁₋₈alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C₆₋₁₂arylC₁₋₆alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; an optionally substituted heteroC₆₋₁₀arylC₁₋₆alkyl group, such as a pyridinylmethyl e.g. pyridin-4-ylmethyl or imidazolylethyl e.g. 2-imidazol-1-ylethyl group; a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C₆₋₁₂arylthioC₁₋₈alkyl group such as an optionally substituted phenylthioethyl group; a C₆₋₁₂arylsulfinylC₁₋₈alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C₆₋₁₂arylsulfonylC₁₋₈alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C₄₋₈imidoC₁₋₈alkyl group such as a

succinimidomethyl or phthalamidoethyl group; a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C₁₋₈alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional
5 substituents present on the Alk⁷ group include R^{13a} substituents described below.

It will be appreciated that in the forgoing list of Alk⁷ groups the point of attachment to the remainder of the compounds of formulae (1) or (2) is via the
10 last described part of the Alk⁷ group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group would be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk⁷ groups, where not
15 specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined for Alk¹. Additionally these alkyl, alkenyl or alkynyl groups may optionally be interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L³.

20 Further, prodrugs of compounds of formula (1) which may be prepared using the process of the invention include cyclic esters where X is a –N(R²)– group in which R² becomes a C₁₋₆alkyl joining chain, especially a –CH₂– or –CH₂CH₂– chain, which is also connected to the acid group R¹ to form a cyclic ester of formula (1a):
25



When present in the group R^x, R^y and/or R^z in compounds of formulae (1) or (2) the linker atom or group represented by L¹ may be any linker atom or group as described above for the linker atom or group L³. In addition L¹ may also be a -Se- atom.

5

When Alk¹ is present in the group R^x, R^y and/or R^z in compounds of formulae (1) or (2) as an optionally substituted aliphatic chain it may be an optionally substituted C₁₋₁₀aliphatic chain. Particular examples include optionally substituted straight or branched chain C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋
10 ₆alkynylene chains.

Particular examples of aliphatic chains represented by Alk¹ include optionally substituted -CH₂-, -(CH₂)₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-, -(CH₂)₃CH₂-, -
15 CH(CH₃)(CH₂)₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂CH₂-, -
(CH₂)₂C(CH₃)₂CH₂-, -(CH₂)₄CH₂-, -(CH₂)₅CH₂-, -CHCH-, -CHCHCH₂-, -
CH₂CHCH-, -CHCHCH₂CH₂-, -CH₂CHCHCH₂-, -(CH₂)₂CHCH-, -CC-, -
CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂- or -(CH₂)₂CC- chains.

Heteroaliphatic chains represented by Alk¹ when present in the group R^x, R^y
20 and/or R^z in compounds of formulae (1) or (2) include the aliphatic chains just described for Alk¹ but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular hetero-atoms or groups include atoms or groups L⁵ where L⁵ is as defined above for L³ when L³ is a linker atom or group. Each L⁵ atom or group may interrupt the aliphatic
25 chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group. Particular examples include optionally substituted -CH₂L⁵-, -CH₂CH₂L⁵-, -L⁵CH₂-, -L⁵CH₂CH₂-, -L⁵CH(CH₃)CH₂-, -
L⁵CH₂CH(CH₃)CH₂-, -L⁵CH₂CH₂CH(CH₃)-, -L⁵C(CH₃)₂CH₂-, -
CH₂L⁵CH₂CH₂-, -(CH₂)₂L⁵CH₂-, -(CH₂)₃L⁵CH₂-, -L⁵(CH₂)₃-, -L⁵(CH₂)₄-, -
30 CH₂L⁵CH₂CHL⁵CH₂- and -(CH₂)₂L⁵CH₂CH₂- chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk¹ include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO₂H, -CO₂R⁹, where R⁹ is an optionally substituted straight or branched C₁₋₆alkyl group as defined above for R⁵, -CONHR⁹, -CON(R⁹)₂, -COR⁹, e.g. -COCH₃, C₁₋₆alkoxy, e.g. methoxy or ethoxy, thiol, -S(O)R⁹, -S(O)₂R⁹, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR⁹ and -N(R⁹)₂ groups. Where two R⁹ groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z in compounds of the invention include optionally substituted C₃₋₁₀cycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀cycloalkyl, e.g. C₃₋₈cycloalkyl or C₃₋₁₀cycloalkenyl, e.g. C₃₋₈cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z include optionally substituted C₃₋₁₀heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀heterocycloalkyl, e.g. C₃₋₇heterocycloalkyl, or C₃₋₁₀heterocycloalkenyl, e.g. C₃₋₇heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L⁵ as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R³ include the optionally substituted polycycloaliphatic groups just described, but with each group additionally containing one, two, three or four L⁵ atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocyclo-aliphatic and heteropolycycloaliphatic groups represented by the group R^3 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, piperidinyl, piperidinone, dioxanyl e.g. 1,3-dioxanyl or 1,4-dioxanyl, morpholinyl, morpholinone, dithianyl, e.g. 1,3-dithianyl or 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group R^3 include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6} alkyl, e.g. methyl, ethyl, propyl or i-propyl, halo C_{1-6} alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6} alkoxy, e.g. methoxy, ethoxy or propoxy, halo C_{1-6} alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6} alkylthio e.g. methylthio, ethylthio or propylthio, or $-(Alk^4)_gR^{10}$ groups in which Alk^4 is a straight or branched C_{1-3} alkylene chain, g is zero or an integer 1 and R^{10} is a $-OH$, $-SH$, $-N(R^{11})_2$, (in which R^{11} is an atom or group as defined herein for R^8) $-CN$, $-CO_2R^{11}$, $-NO_2$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-COR^{11}$, $-CSN(R^{11})_2$, $-N(R^{11})COR^{11}$, $-N(R^{11})CSR^{11}$, $-$

SO₂N(R¹¹)₂, -N(R¹¹)SO₂R¹¹, -N(R¹¹)CON(R¹¹)₂, -N(R¹¹)CSN(R¹¹),
N(R¹¹)SO₂N(R¹¹)₂ or optionally substituted phenyl group. Where two R¹¹
atoms or groups are present in these substituents these may be the same or
different or joined to form a heterocyclic ring as previously described when R⁶
5 and R⁷ are joined together. Optionally substituted phenyl groups include
phenyl substituted by one, two or three of the R¹³ groups described below.

Additionally, when the group R³ is a heterocycloaliphatic group containing one
or more nitrogen atoms each nitrogen atom may be optionally substituted by a
10 group -(L⁶)_p(Alk⁵)_qR¹² in which L⁶ is -C(O)-, -C(O)O-, -C(S)-, -S(O)₂-, -
CON(R⁸)-, -CSN(R⁸)- or SO₂N(R⁸)-; p is zero or an integer 1; Alk⁵ is an
optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer
1; and R¹² is a hydrogen atom or an optionally substituted cycloaliphatic,
heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or
15 heteroaromatic group.

C₁₋₃alkylene chains represented by Alk⁴ include -CH₂-, -CH₂CH₂-, -
CH₂CH₂CH₂-, -CH(CH₃)CH₂- and -CH₂CH(CH₃)- chains.

20 Optionally substituted aliphatic or heteroaliphatic chains represented by Alk⁵
include those optionally substituted chains described above for Alk¹. Optional
substituents which may be present on these groups include those described
above in relation to Alk¹.

25 Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocyclo-
aliphatic groups represented by R¹² include those groups just described for
the group R³. Optional substituents which may be present on those groups
include those described above in relation to R³ cycloaliphatic groups.

30 Aromatic or heteroaromatic groups represented by R¹² include those groups
described herein for the group Ar¹. Optional substituents which may be

present on these groups include those R¹³ optional substituents described hereinafter.

When the group R³ is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar¹.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R³ include one, two, three or more substituents, each selected from an atom or group R¹³ in which R¹³ is -R^{13a} or -Alk⁶(R^{13a})_m, where R^{13a} is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -COR¹⁴ [where R¹⁴ is an -Alk⁶(R^{13a})_m, aryl or heteroaryl group], -CSR¹⁴, -SO₃H, -SOR¹⁴, -SO₂R¹⁴, -SO₃R¹⁴, -SO₂NH₂, -SO₂NHR¹⁴, SO₂N(R¹⁴)₂, -CONH₂, -CSNH₂, -CONHR¹⁴, -CSNHR¹⁴, -CON[R¹⁴]₂, -CSN(R¹⁴)₂, -N(R¹¹)SO₂R¹⁴, -N(SO₂R¹⁴)₂, -NH(R¹¹)SO₂NH₂, -N(R¹¹)SO₂NHR¹⁴, -N(R¹¹)SO₂N(R¹⁴)₂, -N(R¹¹)COR¹⁴, -N(R¹¹)CONH₂, -N(R¹¹)CONHR¹⁴, -N(R¹¹)CON(R¹⁴)₂, -N(R¹¹)CSNH₂, -N(R¹¹)CSNHR¹⁴, -N(R¹¹)CSN(R¹⁴)₂, -N(R¹¹)CSR¹⁴, -N(R¹¹)C(O)OR¹⁴, -SO₂NHet¹ [where -NHet¹ is an optionally substituted C₅₋₇cyclicamino group optionally containing one or more other -O- or -S- atoms or -N(R¹¹)-, -C(O)-, -C(S)-, S(O) or -S(O)₂ groups], -CONHet¹, -CSNHet¹, -N(R¹¹)SO₂NHet¹, -N(R¹¹)CONHet¹, -N(R¹¹)CSNHet¹, -SO₂N(R¹¹)Het² [where Het² is an optionally substituted monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R¹¹)-, -C(O)- or -C(S)- groups], -Het², -CON(R¹¹)Het², -CSN(R¹¹)Het², -N(R¹¹)CON(R¹¹)Het², -N(R¹¹)CSN(R¹¹)Het², aryl or heteroaryl group; Alk⁶ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_n [where n is an integer 1 or 2] or -N(R¹⁵)- groups [where R¹⁵ is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will

be appreciated that when two R¹¹ or R¹⁴ groups are present in one of the above substituents, the R¹¹ or R¹⁴ groups may be the same or different.

When in the group -Alk⁶(R^{13a})_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in -Alk⁶. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk⁶. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk⁶ becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group -NHR¹⁴ [where R¹⁴ is as defined above] or a group -N(R¹⁴)₂ wherein each R¹⁴ group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR¹⁴ or a -SR¹⁴ or -SC(=NH)NH₂ group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula -CO₂Alk⁸ wherein Alk⁸ is a straight or branched, optionally substituted C₁₋₈alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆₋₁₂arylC₁₋₈alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroxyloxyC₁₋₈alkyl

group such as an optionally substituted benzoyloxyethyl or benzoyloxy-propyl group. Optional substituents present on the Alk⁸ group include R^{13a} substituents described above.

- 5 When Alk⁶ is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R⁸)- groups.

10

Aryl or heteroaryl groups represented by the groups R^{13a} or R¹⁴ include mono- or bicyclic optionally substituted C₆₋₁₂aromatic or C₁₋₉hetero-aromatic groups as described above for the group Ar¹. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of
15 formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet¹ or -Het² forms part of a substituent R¹³ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally
20 Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those optional substituents described above in relation to aliphatic chains represented by Alk¹.

- 25 Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, oxazolidinyl,
30 thiazolidinyl, imidazolidinyl or piperidinyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-

carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy,
 hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy,
 pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₄₋₇cycloalkyl, e.g. cyclobutyl,
 cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g.
 5 trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g.
 methylamino, ethylamino or propylamino, C₆₋₁₂arylC₁₋₆alkylamino, e.g.
 benzylamino, 4-fluorobenzyl-amino or 4-hydroxyphenylethylamino, amino (-
 NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g.
 dimethylamino or diethylamino, aminoC₁₋₆alkylamino, e.g. aminoethylamino or
 10 amino-propylamino, optionally substituted Het¹NC₁₋₆alkylamino, e.g. 3-
 morpho-linopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆
 dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g.
 aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆
 15 dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy,
 diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino,
 e.g. 2-hydroxyethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino,
 imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro,
 cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁸
 [where Alk⁸ is as defined above], C₁₋₆alkanoyl e.g. acetyl, propyryl or butyryl,
 20 optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or
 thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), -SO₃Alk⁸, C₁₋₆alkylsulphinyl, e.g.
 methylsulphinyl, ethylsulphinyl or propylsulphinyl, C₁₋₆alkylsulphonyl, e.g.
 methylsulphonyl, ethylsulphonyl or propyl-sulphonyl, aminosulphonyl (-
 SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl,
 25 ethylaminosulphonyl or propylaminosulphonyl C₁₋₆dialkylaminosulphonyl, e.g.
 dimethylaminosulphonyl or diethylamino-sulphonyl, phenylaminosulphonyl,
 carboxamido (-CONH₂), C₁₋₆alkylamino-carbonyl, e.g. methylaminocarbonyl,
 ethylaminocarbonyl or propylamino-carbonyl, C₁₋₆dialkylaminocarbonyl, e.g.
 dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆
 30 alkylaminocarbonyl, e.g. aminoethyl-aminocarbonyl, C₁₋₆alkylaminoC₁₋₆
 alkylaminocarbonyl, e.g. methylamino-ethylaminocarbonyl, C₁₋₆

- 6dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethyl-aminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonyl-amino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, haloC₁₋₆alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylamino-methyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxy-carbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.
- Where desired, two R¹³ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or
5 heteroaromatic group represented by R^3 .

When the groups R^x and R^y are joined together to form an optionally substituted spiro linked cycloaliphatic or heterocycloaliphatic group joined to the cyclobutenone ring as defined by formula (1) it may be any such
10 cycloaliphatic or heterocycloaliphatic group as previously described for R^3 . Optional substituents which may be present on such spiro linked cycloaliphatic or heteroaliphatic groups include those optional substituents as described in relation to R^3 .

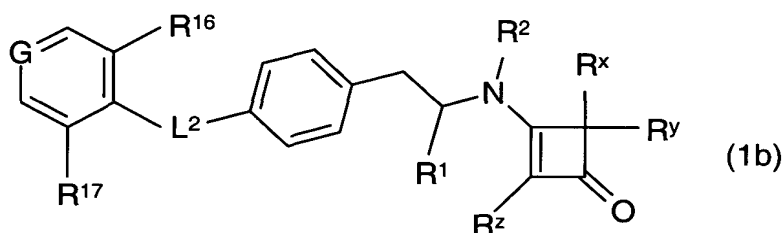
15 The presence of certain substituents in the compounds of formulae (1), (2) or Ar^1W may enable salts of the compounds to be used. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

20 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates,
25 trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium
30 or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

In compounds of formulae (1) or Ar^1W Ar^1 is preferably an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these monocyclic Ar^1 groups include halogen atoms or alkyl, haloalkyl, $-\text{OR}^6$, $-\text{SR}^6$, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{NO}_2$, $-\text{N}(\text{R}^6)\text{COR}^7$ or $-\text{CN}$ groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic groups containing one, two or three, especially one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, 2,7-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups.

The process according to the invention is particularly useful for the preparation of compounds of formula (1b):



wherein $-\text{G}=$ is $-\text{CR}^{18}=$, $-\text{N}=$ or $-\text{N}(\text{O})=$;

R^{16} , R^{17} and R^{18} , which may be the same or different is each a hydrogen atom or an atom or group $-\text{L}^3(\text{Alk}^2)_t\text{L}^4(\text{R}^5)_u$ in which L^3 , Alk^2 , t , L^4 , R^5 and u are as defined previously;

L^2 , R^1 , R^2 , R^x , R^y and R^z are as defined for formula (1);

and the salts, solvates, hydrates and N-oxides thereof.

In one preferred class of compounds of formula (1b) where G is a $-\text{CR}^{18}=\text{}$ group R^{18} is a hydrogen atom. In another preferred class of compounds R^{18} is a preferred atom or group as hereinafter defined for R^{16} , especially a C_{1-6} alkoxy, especially a methoxy or ethoxy, group.

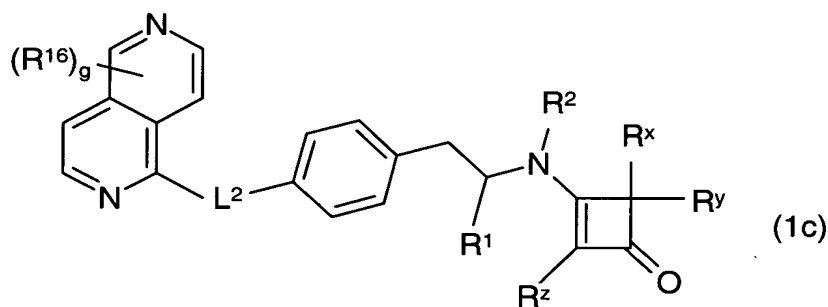
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In another preferred class of compounds of formula (1b) G is a $-\text{N}=\text{}$ or $-\text{N}(\text{O})=\text{}$ group.

R^{16} and R^{17} in compounds of formula (1b) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R^{16} and R^{17} substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-6} alkyl, especially methyl, ethyl or isopropyl, halo C_{1-6} alkyl especially halomethyl, most especially $-\text{CF}_3$, $-\text{CHF}_2$ or $-\text{CH}_2\text{F}$, C_{1-6} alkoxy especially methoxy or etoxy or halo C_{1-6} alkoxy especially halomethoxy, most especially $-\text{OCF}_3$, $-\text{OCHF}_2$ or $-\text{OCH}_2\text{F}$ groups.

15

A further group of compounds particularly prepared according to the process of the invention has the formula (1c):



20

wherein g is the integer 1, 2, 3 or 4;

R^{16} , is an atom or group $-\text{L}^3(\text{Alk}^2)_t\text{L}^4(\text{R}^5)_u$ in which L^3 , Alk^2 , t, L^4 , R^5 and u are as defined previously;

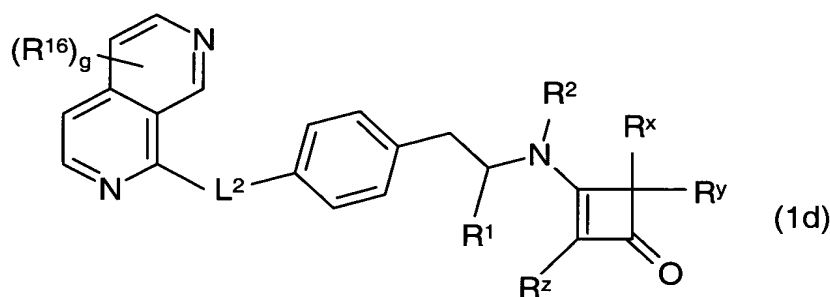
L^2 , R^1 , R^2 , R^x , R^y and R^z are as defined for formula (1);

25

and the salts, solvates, hydrates and N-oxides thereof.

Particular R^{16} substituents when present in compounds of formula (1c) include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl e.g. methyl, ethyl or isopropyl, halo C_{1-6} alkyl, especially halomethyl, most especially $-CF_3$, C_{1-6} alkoxy, especially methoxy, halo C_{1-6} alkoxy, especially halomethoxy, most especially $-OCF_3$, $-CN$, $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^6R^7$) especially $-NHCH_3$ and $-N(CH_3)_2$, $-N(R^6)COCH_3$, especially $-NHCOCH_3$ groups or optionally substituted phenyl, furyl, thienyl, imidazolyl, pyridyl and pyrimidinyl groups.

- 10 The process is also particularly useful for the preparation of compounds of formula (1d):



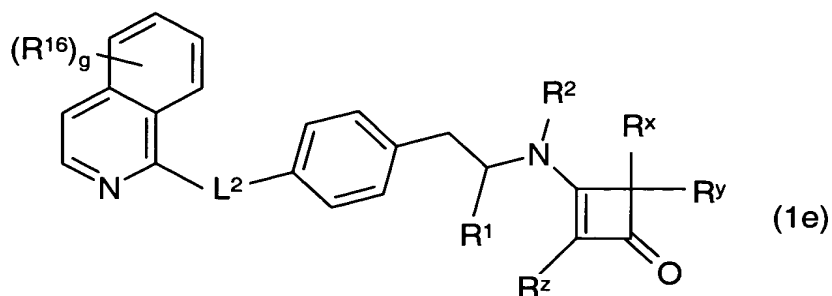
wherein R^{16} , g , L^2 , R^1 , R^2 , R^x , R^y and R^z are as defined for formula (1c);

- 15 and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (1d) may be independently selected from an atom or group $-L^3(Alk^2)_nL^4(R^5)_u$ as previously particularly defined for compounds of formula (1c).

20

A further particularly useful group of compounds prepared according to the process of the invention has the formula (1e):



wherein R^{16} , g , L^2 , R^1 , R^2 , R^x , R^y and R^z are as defined for formula (1c):
and the salts, solvates, hydrates and N-oxides thereof.

- 5 Each R^{16} atom or group in compounds of formula (1e) may be independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^5)_u$ as previously defined for compounds of formula (1c).

10 In one preferred class of compounds of formula (1e) at least one R^{16} atom or group is present at the 3-position of the isoquinoline ring. In a preferred group of compounds of this class R^{16} is an optionally substituted phenyl ring. Optional substituents which may be present on the phenyl ring include halogen atoms, especially fluorine or chlorine atoms, or C_{1-6} alkyl, especially methyl, ethyl or isopropyl, halo C_{1-6} alkyl especially halomethyl, most especially
15 $-CF_3$, $-CHF_2$ or $-CH_2F$, C_{1-6} alkoxy especially methoxy or ethoxy or halo C_{1-6} alkoxy especially halomethoxy, most especially $-OCF_3$, $-OCHF_2$ or $-OCH_2F$ groups.

20 It will be understood that compounds according to formulae (1b), (1c), (1d) and (1e) include, where applicable, the corresponding hydroxy tautomers.

It will be appreciated that the processes used to prepare the compounds of formulae (1b), (1c), (1d) and (1e) each comprise reacting a compound of formula Ar^1W , wherein Ar^1 is the particularly preferred aryl or heteroaryl
25 group, with a compound of formula (2) using the methods as described herein.

In one particular aspect of the invention compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R¹ is a -CO₂H group.

In another particular aspect of the invention compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R¹ is an esterified carboxyl group of formula -CO₂Alk⁷ which may advantageously be used as a prodrug of the active compound. In this class of compound Alk⁷ is preferably a C₁₋₈alkyl group, especially a methyl, ethyl, propyl, i-propyl, butyl, t-butyl, pentyl or neopenyl group; an optionally substituted C₃₋₈cycloalkyl group, especially a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C₃₋₈heterocycloalkyl group especially a tetrahydrofuran-3-yl, pyrrolidinyl e.g. 1-methylpyrrolidinyl such as 1-methylpyrrolidin-3-yl, piperidinyl e.g. 1-methylpiperidinyl such as 1-methylpiperidin-4-yl, tetrahydropyranyl e.g. tetrahydropyran-4-yl or 2-oxo-[1,3]dioxol-4-yl e.g. 5-methyl-2-oxo-[1,3]dioxol-4-yl group; an optionally substituted C₆₋₁₀aryl group, especially a phenyl group; an optionally substituted C₆₋₁₀arylC₁₋₆alkyl group, especially a benzyl group; an optionally substituted heteroC₆₋₁₀arylC₁₋₆alkyl group, especially a pyridinylC₁₋₃alkyl group such as pyridinylmethyl e.g. pyridin-4-ylmethyl or pyridinylethyl e.g. pyridine-4-ylethyl or a imidazolylC₁₋₃alkyl group such as imidazolylethyl e.g. 2-imidazol-1-ylethyl or imidazolylpropyl e.g. 2-imidazol-1-ylpropyl group; an optionally substituted hydroxyC₁₋₆alkyl group, especially a hydroxyethyl e.g. 2-hydroxyethyl or hydroxypropyl e.g. 3-hydroxypropyl or 2,3-dihydroxypropyl group; an optionally substituted C₃₋₈heterocycloalkylC₁₋₆alkyl group, especially a morpholinyl-N-ethyl group; an optionally substituted N-di-C₁₋₈alkylaminoC₁₋₈alkyl group, especially a N-dimethylaminoethyl or N-diethylaminoethyl group; or an optionally substituted C₁₋₆alkyloxyC₁₋₆alkyl group, especially a methoxyethyl group. Especially preferred esterified carboxyl groups include -CO₂CH₃, -CO₂CH₂CH₃, -CO₂CH₂CH₂CH₃, -CO₂CH(CH₃)₂ and -CO₂C(CH₃)₃ groups.

The process is especially useful for preparing esterified carboxyl groups (-CO₂Alk⁷) which are selected from -CO₂(hydroxyC₁₋₆alkyl), especially -CO₂CH₂CH₂OH or -CO₂CH₂CH₃.

- 5 In general in compounds of formula (1), (1b), (1c), (1d), (1e), (2), (4) and (5) R² is preferably a hydrogen atom.

In one preferred aspect compounds of formula (1b) are prepared wherein L² is a -CON(R⁴)- group [where R⁴ is preferably a hydrogen atom or a C₁₋₃alkyl group], especially a -CONH- group. In this class of compounds -G= is
10 preferably -N= or -N(O)=. Most preferably G is -N=.

In another preferred aspect compounds of formulae (1c), (1d) and (1e) are prepared wherein L² is a -N(R⁴)- group [where R⁴ is preferably a hydrogen atom or a C₁₋₃alkyl group]. An especially preferred -N(R⁴)- group is -NH-.
15

In one generally preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^x, R^y and/or R^z is an optionally substituted alkyl group, most preferably an optionally substituted C₁₋₈alkyl group such as
20 a methyl, ethyl, n-propyl, i-propyl, n-butyl, n-heptyl, or n-hexyl group. Particularly preferred optional substituents which may be present on such R^x, R^y and/or R^z alkyl groups include halogen atoms, especially fluorine or chlorine atoms, C₁₋₆alkoxy groups, especially methoxy, haloC₁₋₆alkoxy groups, especially -OCF₃, -CN, -CO₂CH₃, -NO₂, substituted amino (-NR⁶R⁷)
25 especially -NHCH₃ and -N(CH₃)₂ and optionally substituted phenyl groups where the optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁₋₆alkyl e.g. methyl, ethyl or i-propyl, haloC₁₋₆alkyl especially halomethyl, most especially -CF₃, C₁₋₆alkoxy especially methoxy or haloC₁₋₆alkoxy, especially halomethoxy, most especially -OCF₃, -
30 CN, -CO₂CH₃, -NO₂, amino (-NH₂), substituted amino (NR⁶R⁷) especially -NHCH₃ and -N(CH₃)₂ and -N(R⁶)COCH₃, especially -NHCOCH₃ groups.

In one generally preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X , R^Y and/or R^Z is an optionally substituted alkyl group, most preferably an optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, n-heptyl, or n-hexyl group.

5 Particularly preferred optional substituents which may be present on such R^X , R^Y and/or R^Z alkyl groups include halogen atoms, especially fluorine or chlorine atoms, C_{1-6} alkoxy groups, especially methoxy, halo C_{1-6} alkoxy groups, especially $-OCF_3$, $-CN$, $-CO_2CH_3$, $-NO_2$, substituted amino ($-NR^6R^7$) especially $-NHCH_3$ and $-N(CH_3)_2$ and optionally substituted phenyl groups
10 where the optional substituents are as herein defined above.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^Z is a hydrogen atom.

15 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X is a hydrogen atom.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^Z is a halogen atom, especially a fluorine,
20 chlorine, bromine or iodine atom, most especially a chlorine or bromine atom.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^Z is a group $-L^1(Alk^1)_nR^3$. In this class of compounds L^1 is preferably a covalent bond or an $-O-$, $-S-$ or $-Se-$ atom or $-S(O)-$ or $-N(R^8)-$, especially $-NH-$ or $-N(CH_3)-$ group. Most preferably L^1 is a $-S-$ atom or $-S(O)-$ group. In this class of compounds R^3 is preferably a hydrogen atom or an optionally substituted C_{3-10} cycloaliphatic, especially C_{3-7} cycloalkyl group, most especially an optionally substituted cyclopentyl, cyclohexyl or cycloheptyl group; or an optionally substituted C_{3-10} heterocycloaliphatic, especially C_{3-7} heterocycloalkyl group, most especially
30 an optionally substituted piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, dithianyl or pyrazolidinyl group, or an optionally substituted C_{6-12} aromatic

group, preferably an optionally substituted phenyl group or an optionally substituted C₁₋₉heteroaromatic group, preferably an optionally substituted monocyclic C₁₋₉heteroaromatic group, most preferably a 5- or 6-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, especially an optionally substituted furyl, thienyl, imidazolyl e.g. 1-methylimidazol-2-yl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or pyrazinyl group. Optional substituents which may be present on such heterocycloaliphatic groups include those substituents as described hereinafter when R^x and R^y are joined to form an optionally substituted spiro linked heterocycloaliphatic group. Optional substituents which may be present on such aromatic and heteroaromatic groups include those substituents as described hereinbefore in relation to R¹⁶ substituents in compounds of formula (1b). In one preferred group of compounds of this class n is zero. In another preferred group of compounds of this class L¹ is a covalent bond and n is zero. In this group of compounds R³ is preferably an optionally substituted C₃₋₁₀cycloaliphatic, C₃₋₁₀heterocycloaliphatic, C₆₋₁₂aromatic or monocyclic C₁₋₉heteroaromatic group as just described. In a further preferred group of compounds of this class n is the integer 1 and Alk¹ is preferably an optionally substituted aliphatic chain, most preferably an optionally substituted C₁₋₆alkylene chain, especially a -CH₂-, -CH₂CH₂- or -CH₂CH(CH₃)- chain. In a further preferred group of compounds of this class L¹ is a covalent bond, n is the integer 1 and Alk¹ is preferably an optionally substituted aliphatic chain, most preferably an optionally substituted C₁₋₆alkylene chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH(CH₃)- chain. In a further preferred group of compounds of this class L¹ is a preferred atom or group as just described, most especially a -S- atom, n is the integer 1 and Alk¹ is preferably an optionally substituted aliphatic chain, most preferably an optionally substituted C₁₋₆alkylene chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH(CH₃)- chain. In this class of compounds R³ is preferably a hydrogen atom.

Most especially preferred R^Z groups which may be prepared using the process of the invention include a hydrogen or halogen atom, especially fluorine, chlorine, bromine or iodine atom or a group of formula $-L^1(Alk^1)_nR^3$ as just defined, especially an alkyl group as previously described or a hydroxyl (-OH); C_{1-6} alkoxymethoxy, ethoxy or i-propoxy; C_{3-7} cycloalkyl, especially cyclopentyl or cyclohexyl; C_{1-6} alkylsulfanyl, especially methyl- ethyl- or i-propylsulfanyl; C_{1-6} alkylsulfinyl, especially methyl- ethyl- or i-propylsulfinyl; C_{3-7} heterocycloalkyl, especially piperidinyl most especially piperidin-3-yl such as 1-methylpiperidin-3-yl or dithianyl especially [1,3]dithian-2-yl; C_{6-12} arylselenenyl, especially phenylselenenyl; C_{6-12} arylsulfanyl, especially phenylsulfanyl or pentafluorophenylsulfanyl; monocyclic C_{1-9} heteroaromaticsulfanyl, especially tetrazol-5-ylsulfanyl most especially 1-methyl-1H-tetrazol-5-ylsulfanyl or imidazolylsulfanyl especially imidazol-2-ylsulfanyl most especially 1-methyl-1H-imidazol-2-ylsulfanyl; monocyclic C_{1-9} heteroaromatic, especially pyridinyl most especially pyridin-3-yl, 1-methylpyridinium or pyrazinyl especially pyrazin-2-yl; or a $C_{6-12}arylC_{1-3}alkyl$, especially benzyl group.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Z is each a hydrogen atom.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X is a hydrogen atom and R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom, or R^Z is a group $-L^1(Alk^1)_nR^3$ as just described.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y is each a hydrogen atom and R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom, or R^Z is a group $-L^1(Alk^1)_nR^3$ as just described.

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X is a hydrogen atom and R^Y is an optionally substituted alkyl group as just described for generally preferred alkyl groups.

- 5 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Z is each a hydrogen atom and R^Y is an optionally substituted alkyl group as just described.

- 10 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X is a hydrogen atom, R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom or R^Z is a group $-L^1(Alk^1)_nR^3$, especially a group as just particularly described, and R^Y is an optionally substituted alkyl group as just described for generally preferred alkyl groups.

15

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X is a hydrogen atom and R^Y and R^Z is each an optionally substituted alkyl group as just described for generally preferred alkyl groups.

20

In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y is each an optionally substituted alkyl group as just described for generally preferred alkyl groups.

- 25 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y is each an optionally substituted alkyl group as just described for generally preferred alkyl groups and R^Z is a hydrogen atom.

- 30 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y is each an optionally substituted alkyl group as just described for generally preferred alkyl groups and R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most

especially a chlorine or bromine atom, or R^Z is a group $-L^1(Alk^1)_nR^3$ as just described.

5 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X , R^Y and R^Z is each an optionally substituted alkyl group as just described for generally preferred alkyl groups.

10 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y are joined to form an optionally substituted spiro linked cycloaliphatic group particularly a C_{3-10} cycloaliphatic group, most particularly a C_{3-8} cycloalkyl group, especially an optionally substituted cyclopentyl cyclohexyl, cycloheptyl or cyclooctyl group, or a C_{3-8} cycloalkenyl group, especially an optionally substituted cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl group group. Particularly
15 preferred optional substituents which may be present on such spiro linked cycloaliphatic groups include halogen atoms, especially fluorine or chlorine atoms, C_{1-6} alkyl groups, especially methyl, ethyl, propyl or i-propyl, C_{1-6} alkoxy groups, especially methoxy or ethoxy, halo C_{1-6} alkoxy groups, especially $-OCF_3$, $-CN$, $-CO_2CH_3$, $-NO_2$ and substituted amino ($-N(R^{11})_2$),
20 especially $-NHCH_3$ and $-N(CH_3)_2$ groups. In a preferred group of compounds of this class R^Z is a hydrogen atom. In another preferred group of compounds of this class R^Z is an alkyl group as just described. In a further preferred group of compounds of this class R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom,
25 particularly a bromine atom. In a still further preferred group of compounds of this class R^Z is a group $-L^1(Alk^1)_nR^3$ as just described.

30 In another preferred aspect compounds of formulae (1), (1b), (1c), (1d) and (1e) are prepared wherein R^X and R^Y are joined to form an optionally substituted spiro linked heterocycloaliphatic group, particularly an optionally substituted C_{3-10} heterocycloaliphatic group, most particularly an optionally substituted C_{3-7} heterocycloalkyl group, especially an optionally substituted

C₃₋₇heterocycloalkyl group containing one or two -O-, -S-, -S(O)-, -S(O)₂-, -NH- or -C(O)- heteroatoms or heteroatom-containing groups. Especially preferred optionally substituted heterocycloaliphatic groups include optionally substituted 5- and 6-membered heterocycloalkyl groups containing one

 5 heteroatom or heteroatom-containing group as just described, especially optionally substituted pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl tetra-hydrothiopyran-1-oxide or tetrahydrothiopyran-1,1-dioxide groups. Particularly preferred optional

 10 substituents which may be present on such spiro linked heterocycloaliphatic groups include halogen atoms, especially fluorine or chlorine atoms, C₁₋₆alkyl groups, especially methyl, ethyl, propyl or i-propyl, C₁₋₆alkoxy groups, especially methoxy or ethoxy, haloC₁₋₆alkoxy groups, especially -OCF₃, -CN, -CO₂CH₃, -NO₂ and substituted amino (-N(R¹¹)₂), especially -NHCH₃ and -

 15 N(CH₃)₂ groups. In addition when the spiro linked heterocycloaliphatic group contains a nitrogen atom this may be substituted by a group -(L⁶)_p(Alk⁵)_qR¹² where L⁶ is preferably -C(O)- or -S(O)₂-, Alk⁵ is preferably an optionally substituted C₁₋₆alkylene chain, especially a -CH₂-, -(CH₂)₂- or -CH(CH₃)CH₂- chain or an optionally substituted heteroC₁₋₆alkylene chain, especially -

 20 CH₂L⁵-, -CH₂CH₂L⁵-, -L⁵CH₂- or -L⁵CH₂CH₂ chain where L⁵ is an -O- or -S- atom or -NH or -N(CH₃)- group and R¹² is a hydrogen atom or an optionally substituted phenyl ring where preferred optional substituents include those atoms and groups as defined hereinbefore for R¹⁶ in relation to formula (2b). In one preferred group of compounds of this class R^Z is a hydrogen atom. In

 25 another preferred group of compounds of this class R^Z is an alkyl group as just described. In a further preferred group of compounds of this class R^Z is a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, most especially a chlorine or bromine atom. In a still further preferred group of compounds of this class R^Z is a group -L¹(Alk¹)_nR³ as just described.

30

The process is particularly suitable for the preparation of the following compounds:

(2*S*)-2-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoic acid;

(2*S*)-2-(2-bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]propionic acid;

- 5 (2*S*)-2-[(2-isopropylsulfanyl-3-oxo-7-oxa-spiro[3.5]non-1-en-1-yl)amino]-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]propanoic acid
and the salts, solvates, hydrates and N-oxides thereof.

- 10 The process is most especially suitable for the preparation of the following compounds:

ethyl (2*S*)-2-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate;

ethyl (2*S*)-2-(2-bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]propanoate;

- 15 ethyl (2*S*)-2-[(2-isopropylsulfanyl-3-oxo-7-oxa-spiro[3.5]non-1-en-1-yl)amino]-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]propanoate;
and the salts, solvates, hydrates and N-oxides thereof.

The process is also most especially suitable for the preparation of:

- 20 2-hydroxyethyl (2*S*)-2-(2-bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate;
and the salts, solvates, hydrates and N-oxides thereof.

- 25 Compounds of formulae (1), (1b), (1c), (1d) and (1e) are potent and selective inhibitors of $\alpha 4$ integrins. The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders including inflammation in which the extravasation of leukocytes plays a role. Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or
30 polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease. The use and formulation of the compounds is

more particularly described in our co-pending International Patent Application PCT/GB 02/00206.

5 For convenience the description hereinafter refers to the preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formulae (1b), (1c), (1d) and (1e).

10 Thus in the process of the invention a substituted 4-aminophenylalanine of formula (2) is reacted with a compound Ar^1W to give a compound of formula (1). Suitable conditions for this reaction depend upon the nature of the group W.

15 Thus when W is the group X^1 the reaction may be carried out in the presence of an acid, such as a Bronsted acid e.g. hydrogen chloride. The acid may be generated in situ as a reaction by-product or may be added at the start of the reaction as an initiator e.g. catalytic amount of hydrogen chloride. The reaction may be performed in a variety of solvents such as alcohols e.g. ethanol, ethers e.g. tetrahydrofuran, 2-methoxyethyl ether, 1,4-dioxane, acetic acid, water, acetonitrile, substituted amides such as N,N-dimethylformamide or acetates e.g. ethyl acetate.

In one particular aspect of the process X^1 is a halogen atom, especially a chlorine or bromine atom.

25 Compounds of formula Ar^1X^1 may be prepared from alcohols of formula Ar^1OH using methods known to those skilled in the art e.g. by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride at an elevated temperature e.g. 110°C or by reaction with hydrogen halide e.g. hydrogen bromide.

30

Intermediates of formulae Ar^1OH or Ar^1X^1 may be prepared using methods as described in co-pending International Patent Application Number WO 02/069393.

When in the process of the invention W is the group -COX^2 and X^2 is a halogen atom such as a chlorine atom the reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or a dipolar aprotic solvent such as an amide, e.g. dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran or an ester e.g. ethyl acetate at for example ambient temperature. The acid chlorides Ar^1COCl may be prepared from the corresponding acid using methods known to those skilled in the art.

Alternatively, the acylation may be carried out under the same conditions with an acid (i.e. where X^2 is -OH) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction.

It will be appreciated by those skilled in the art that acid groups may also be activated by the formation of a reactive ester e.g. ethyl or p-nitrophenyl ester.

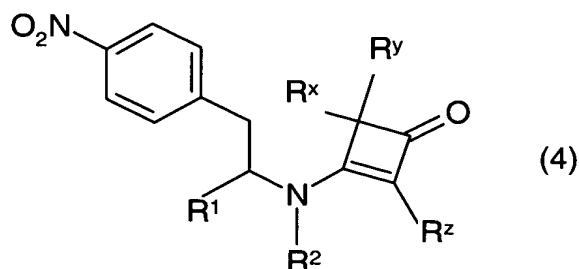
Alternatively when in the process of the invention W is the group $\text{-SO}_2\text{X}^3$ the reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at for example ambient temperature.

Intermediate compounds of formula (2) are novel and form a further aspect of the invention.

One particularly useful compound of formula (2) for use in the process is:

3-(4-aminophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamino)-propionic acid hydroxyethyl ester.

In a further aspect of the invention intermediates of formula (2) may be prepared by reduction of a compound of formula (4):



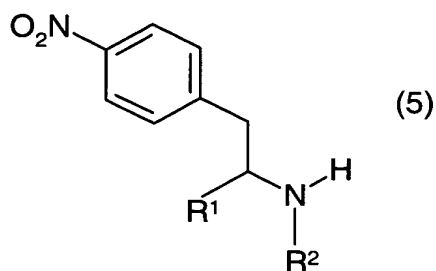
wherein R^1 , R^2 , R^x , R^y and R^z are as herein defined.

Suitable conditions may involve catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol or ethanol or an ester e.g. ethyl acetate. The reaction may be performed at atmospheric pressure or up to a pressure of 10 Bar. Alternatively chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid may be employed. The amine thus formed may be alkylated using conditions known to those skilled in the art to give a compound of formula (2) wherein R^4 is an optionally substituted straight or branched C_{1-6} alkyl group.

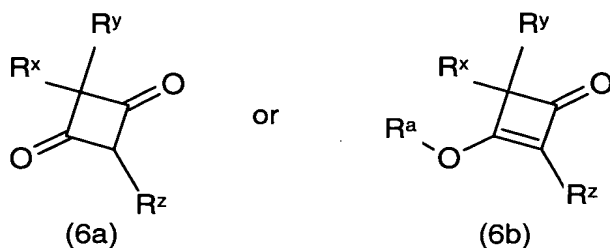
Intermediate compounds of formula (4) are novel and form a further aspect of the invention.

One particularly useful compound of formula (4) for use in the process is:
3-(4-nitrophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamino)propionic acid hydroxyethyl ester.

Thus according to a further aspect of the invention intermediates of formula (4) may be prepared by reaction of a compound of formula (5):



wherein R^1 and R^2 are as herein defined;
with a compound of formula (6a) or (6b):



- 5 wherein R_x , R_y and R_z are as herein defined and R^a represents a C_{1-6} alkyl group or a silyl group. Particular silyl groups include alkylsilyl groups such as a *t*butyldimethylsilyl or trimethylsilyl group.

- 10 The reaction may be performed in an inert solvent or mixture of solvents, for example a hydrocarbon such as an aromatic hydrocarbon e.g. benzene or toluene, a halogenated hydrocarbon such as 1,2-dichloroethane, or dichloromethane, or an ester e.g. ethyl acetate at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine of formula (5) is used, an organic base such as diisopropylethylamine
- 15 or triethylamine may be added.

Intermediates of formulae (6a) or (6b) may be prepared using methods as described in International Patent Application Number WO 02/069393.

- 20 It will be appreciated that intermediates of formula (5) where not commercially available may be prepared using methods known to those skilled in the art. For example intermediates of formula (5) in which R^1 is a $-\text{CO}_2\text{Alk}^7$ group may be prepared by esterification of the corresponding amino acid.

- 25 In one aspect of the process R^1 is especially the group $-\text{CO}_2\text{Alk}^7$.

In another aspect of the process R^4 is especially a hydrogen atom.

It will be appreciated that intermediates, such as intermediate Ar^1W , (5), (6a) or (6b), if not available commercially, may also be prepared by methods known to those skilled in the art following procedures set forth in references such as Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-19 (John Wiley and Sons, 1999), Comprehensive Heterocyclic Chemistry, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-7, 1995 (Pergamon), Comprehensive Organic Synthesis, Ed. Trost and Fleming, Volumes 1-9, (Pergamon, 1991), Encyclopedia of Reagents for Organic Synthesis Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley and Sons, 1992).

Where desired the process according to the invention may be extended by optionally employing one or more subsequent reactions to convert a compound of formula (1) to a further compound of formula (1) as described hereinafter.

Further, compounds of formula (1) in which R^Z is a halogen atom may be obtained from compounds of formula (1) in which R^Z is a hydrogen atom by reaction with a halogen source such as bromine or a halosuccinamide e.g. chloro or bromosuccinamide. The reaction may be performed in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an ester e.g. ethyl acetate at a temperature from about 0° to 30° . When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine in the presence of a halogenated hydrocarbon e.g. dichloromethane.

Further, compounds of formula (1) in which R^Z is a group $-L^1(Alk^1)_n(R^3)_v$ in which L^1 is for example a Se, S, O or N(R^8) may be prepared by reaction of an intermediate of formula $HL^1(Alk^1)_n(R^3)_v$ with a compound of formula (1) in which R^Z is a hydrogen atom. The reaction may be performed in an organic solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at around room temperature optionally in the presence of a base such as an amine e.g. triethylamine. When R^Z is the group $-S(Alk^1)_n$ the reaction may be achieved using a compound of formula $-HalS(Alk^1)_n$ where Hal is a halogen atom, for example, chlorine.

It will be appreciated by one skilled in the art that the group R^Z may also be derivatised, for example as described above, in intermediates preceding the compounds of formula (1).

Further the compounds of formula (1) which contain the group Alk^7 may be interconverted to give acids or further derivatives (e.g. esters) or biosteres of formula (1).

Thus the process may be used to obtain a compound of formula (1) in which R^1 is a $-CO_2H$ group by hydrolysis of an ester of formula (1) wherein R^1 is the group $-CO_2Alk^7$. The hydrolysis may be performed using either an acid or a base depending on the nature of Alk^7 , for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used. The acids thus formed may then be further derivatised, for example by esterification, using standard methods known to those skilled in the art, such as reaction with an alcohol of formula $-HOAlk^7$ in the presence of an acid catalyst e.g. p-toluenesulfonic acid. Alternatively a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, may be employed,

advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively an ester of formula (1) may undergo transesterification, preferably in the presence of an acid catalyst, to give another ester of formula (1).

5

In the above processes, compounds containing a basic centre may be isolated and/or crystallised by the formation of a salt, which may offer an improvement in purity. Suitable salts include, but are not limited to oxalate or di-p-toluoyl-D-tartrate.

10

It will be appreciated that the compounds of formula (1), such as those as formed in the process as defined herein, or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or any preceding intermediates where appropriate functional groups exist in these compounds.

20

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

25

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

30

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

- 5 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance
10 where the diastereomer is a salt.

- In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate
15 chiral intermediate in one of the processes of the invention described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

- 20 Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

- 25 The following examples illustrate the present invention in more detail; however, they are not intended to limit its scope in any manner.

All temperatures are in °C. The following abbreviations are used:

- | | |
|----------------------------|------------------------------------|
| EtOAc - ethyl acetate; | DCM - dichloromethane; |
| MeOH - methanol; | HOAc - acetic acid; |
| 30 EtOH - ethanol; | Et ₂ O – diethyl ether; |
| DMSO - dimethylsulphoxide; | DMF - N,N-dimethylformamide; |
| THF - tetrahydrofuran, | HOBT - 1-hydroxybenzotriazole |
| nBuLi – n-butyl lithium | LDA - lithium diisopropylamide |

EDC – 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

All NMR's were obtained either at 300MHz or 400MHz.

All Intermediates and Examples were named with the aid of Beilstein Autonom
(available from MDL Information Systems GmbH, Therdor-Heuss-Allee 108D
60486, Frankfurt, Germany) or were given names that seemed consistent,
with the exception that propanoates were named by the IUPAC name rather
than the trivial name (propionate) and isonicotinoyl (trivial name) is used in
place of pyridine-4-carbonyl.

INTERMEDIATE 1

3,5-Dichloropyridine-4-carboxylic acid

A solution of 3,5-dichloropyridine (5.00g, 33.8mmol) in THF (25ml) was added
to a solution of LDA [generated from nBuLi (2.5M solution in hexanes, 14.9ml,
37.2mmol) and diisopropylamine (4.10g, 5.7ml, 40.6mmol)] in THF (25ml) at -
78° under nitrogen, to give a yellow/brown slurry. The reaction was stirred for
30min at -78° then CO₂ gas was bubbled through to give a clear brown
solution that slowly gave a precipitate, warmed to RT over 2h, then quenched
with water (20ml) and partitioned between Et₂O (100ml) and 1M NaOH
(100ml). The aqueous layer was separated and acidified to pH 1 with
concentrated hydrochloric acid and then extracted with 10% MeOH in DCM
(100mlx3). The combined organic layers were dried (MgSO₄) and the solvent
removed under vacuum to give a brown solid that was recrystallised from
ethanol and dried under vacuum to give the title compound as pinkish crystals
(2.63g, 41%). δ H (DMSO-d₆) 8.74 (2H, s). δ C (DMSO-d₆) 163.5, 147.7,
141.0, 126.7.

INTERMEDIATE 2

3,5-Dichloroisonicotinoyl chloride

Intermediate 1 (150 g) was suspended in toluene (450 mL) containing
dimethyl formamide (1.5 mL). As this mixture was boiled under reflux, thionyl
chloride (132.8 g) was charged to it over 1 h. The reaction was complete after
a further 2.0 h at 110°C. The solvent was removed at atmospheric pressure

and then the residue was vacuum distilled, giving the title compound fraction as a water white oil that partially crystallised on standing (151.3g, 92.0% yield, b.p 70-72°C/1.0 mmHg). δ H (CDCl₃): 8.64 (2H, s). ESI⁺ (*m/z*+1) 209.9

5 INTERMEDIATE 3

3-Cyano-4-(2-(*N,N*-dimethylamino)ethylen-1-yl)pyridine

A solution of 4-methyl-3-cyanopyridine [prepared according to Ref: J. Prakt. Chem. 338, 663 (1996)], (8.0g, 67.8mmol) and *N,N*-dimethylformamide diethyl acetal (11.0g, 74.8mmol) in dry DMF (50ml) was stirred at 140^o under N₂ for 2
10 days. An additional portion of *N,N*-dimethylformamide diethyl acetal (5g) was added and stirred at 140^o for 4h. The volatiles were removed *in vacuo* and the obtained dark oil partitioned between EtOAc (300ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3x100ml). The combined organic extracts were washed with brine (30ml),
15 dried (Na₂SO₄), treated with activated charcoal, filtered and evaporated *in vacuo* to afford essentially pure title compound as a dull orange solid (10.1g, 85%). δ H (CDCl₃) 8.49 (1H, s), 8.25 (1h, d, \underline{J} 5.9Hz), 7.29 (1H, d, \underline{J} 13.2Hz), 7.09 (1H, d, \underline{J} 5.9Hz), 5.25 (1H, d, \underline{J} 13.2Hz) and 2.99 (6H, s); $\underline{m/z}$ (ES⁺, 70V) 174 (MH⁺).

20

INTERMEDIATE 4

1-Hydroxy-2,7-naphthyridine hydrochloride salt

HCl gas was bubbled through a stirred solution of Intermediate 3 (6.2g, 3.58mmol) in glacial acetic acid (50ml) and water (0.64ml, 3.55mmol) for 1-
25 2min. The reaction mixture was stirred in a stoppered flask at 40^o for 18h. The volatiles were removed *in vacuo* affording a dark residue, which was treated with water (3x20ml) and re-evaporated *in vacuo*. The obtained dark semi-solid was treated with 40ml warm ethanol, ice-cooled, and the undissolved solid collected by filtration affording the title compound as a green coloured solid
30 (5.2g, 80%) δ H (DMSO-d₆) 12.5 (1H, br s), 9.38 (1H, s), 8.84 (1H, d, \underline{J} 7.0Hz), 8.15 (1H, d, \underline{J} 7.0Hz), 7.89 (1H, br dd, \underline{J} 7.0, 5.0Hz) and 6.85 (1H, d, \underline{J} 7.0Hz); $\underline{m/z}$ (ES⁺, 70V), 147 (MH⁺).

INTERMEDIATE 5

1-Chloro-2,7-naphthyridine

Intermediate 4 (5.2g, 28.5mmol) was stirred with phosphorous oxychloride (75ml) at 110° for 24h. The volatiles were removed *in vacuo* affording a dark oil which was poured into an ice-bath cooled mixture of saturated aqueous NaHCO₃ (100ml containing 20g solid NaHCO₃) and EtOAc (100ml). After thorough mixing the phases were separated and the aqueous layer re-extracted with EtOAc (2x75ml). The combined organic extracts were washed with brine (15ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a yellow solid (4.0g, 85%) δ H (CDCl₃) 9.45 (1H, s), 8.81 (1H, d, J 5.7Hz), 8.47 (1H, d, J 5.7Hz), 7.66 (1H, d, J 5.7Hz) and 7.60 (1H, d, J 5.7Hz); m/z (ES⁺, 70V) 165 and 167 (MH⁺).

INTERMEDIATE 6

3-Ethoxy-7-oxaspiro[3.5]non-2-en-1-one

Tetrahydropyranyl-4-carboxylic acid (14.7g, 0.11mol) and DMF (0.5ml) in DCM (150ml) was treated dropwise with oxalyl chloride (1.1eq, 10.9ml, 0.12mol). After 1h the reaction mixture was concentrated *in vacuo* and the residual slurry was diluted with Et₂O (200ml) and the resulting precipitate removed by filtration. The filtrate was treated with ethoxyacetylene (40%w/w solution in hexanes, 1.3eq, 18ml) followed dropwise with triethylamine (25ml, 0.19mol) and the reaction stirred for 11d. Filtration and concentration of the filtrate *in vacuo* followed by chromatography (SiO₂, 5:1 EtOAc:hexanes) gave the title compound as a pale yellow oil (12.1g, 59%). δ H (CDCl₃, 300K) 4.85 (1H, s), 4.23 (2H, q, J 7.1Hz), 3.89-3.75 (4H, m), 1.88-1.79 (4H, m), 1.47 (3H, t, J 7.1Hz); m/z (ES⁺, 70V) 182.9 (MH⁺).

INTERMEDIATE 7

7-Oxaspiro[3.5]nonane-1,3-dione

Intermediate 6 (12.1g, 0.067mol) and 2M hydrochloric acid (26ml) were stirred vigorously for 24h at room temperature. The resulting solution was

concentrated to dryness and the residual slurry was washed with Et₂O (25ml) to give the title compound as an off-white powder (8.93g, 0.062mol). δ H (DMSO d₆, 300K) 4.80 (2H, s), 3.78 (4H, t, \underline{J} 5.5Hz), 2.62 (4H t \underline{J} 5.5Hz); m/z (ES⁺, 70V) 154.9 (MH⁺).

5

INTERMEDIATE 8

3-(4-Nitrophenyl)-2(S)-(3-oxospiro[3.5]non-1-en-1-ylamino)propionic acid thyl ester

Method A

- 10 To a stirred solution of 4-nitro-(L)-phenylalanine ethyl ester hydrochloride salt (23.0 g) (CAS No. 58816-66-3) in dichloromethane (230 mL) and water (230 mL), was added slowly 46-48 % sodium hydroxide solution (7.7 g, 1.1 mol eqs). The layers were separated and the aqueous phase extracted with dichloromethane (100 mL). The combined dichloromethane layers were
- 15 washed with water (100 mL) and saturated brine (100 mL). The organic phase was dried (MgSO₄) prior to evaporation *in vacuo* to give 4-nitro-(L)-phenylalanine ethyl ester in quantitative yield. The free nitro-ester was dissolved in fresh dichloromethane (120 mL) and spiro[3,5]nonane-1,3-dione (CAS No 455264-97-8) (12.9 g) [see Wasserman, H.H. *et al*, J. Org. Chem.,
- 20 38, 1451-1455 (1973)] was added portion-wise with stirring. Conversion to product was complete after 16 h (HPLC). The reaction mixture was diluted with dichloromethane (120 mL), washed with 11% sodium bicarbonate solution (100 mL), saturated brine (100 mL) and then dried (MgSO₄). The title compound was isolated in quantitative yield after removal of solvent *in vacuo*
- 25 (32.4g, viscous oil that crystallised slowly; m.p. 120°C). δ H (DMSO d₆) 8.39 (1H, d), 8.17 (2h, d), 7.56 (2H, d), 4.33 (1H, s), 4.31 (1H, m), 4.14 (2H, q), 3.29 (1H, dd), 3.15 (1H, dd), 1.43-1.70 (8H, m), 1.30 (1H, m), 1.15 (3H, t + 1H, m). ESI⁺ ($m/z+1$) 373.3

Method B

- 30 4-nitro-(L)-phenylalanine ethyl ester hydrochloride salt (100g) was suspended in ethyl acetate (590 mL) and washed with 16.5% potassium carbonate solution (150 mL) at 25-30°C, followed by saturated brine (70 mL). The organic layer was then charged over 10 minutes to a slurry of

spiro[3,5]nonane-1,3-dione (61.0 g) in ethyl acetate (310 mL), and the whole stirred out at 20-25°C for 16 h. Following a satisfactory HPLC completion check, the reaction mixture was washed sequentially with 5% potassium carbonate solution (70 mL) and deionised water (70 mL). Wet ethyl acetate (672 g) was distilled out at atmospheric pressure from the organic phase; this operation also served to dry the residue. The concentrate was cooled to 30°C prior to slow addition of heptane (88 mL), which caused the mixture became turbid. After seeding with authentic product, the preparation was left to crystallise. Once this process was underway, the mixture was cooled further to 0-5°C and diluted with more heptane (190 mL). The title compound was filtered off, washed with cold 30% ethyl acetate in heptane (2 x 270 mL), and then dried *in vacuo* at 50°C to give off-white crystals (m.p. 121.5-123.5°C, 131.2 g, 96.7% yield). ¹H NMR (D₆-DMSO): 1.12 (1H, m); 1.18 (3H, t); 1.32 (1H, m); 1.57 (8H, m); 3.13 (1H, dd); 3.31 (1H, dd); 4.14 (2H, q); 4.33 (1H, m); 4.35 (1H, s); 7.54 (2H, d); 8.17 (2H, d); 8.4 (1H, d) ppm.

INTERMEDIATE 9

3-(4-Aminophenyl)-2(S)-(3-oxospiro[3.5]non-1-en-1-ylamino)propionic acid ethyl ester

Method A

A solution of Intermediate 8 (30 g) in absolute ethanol (300 mL) was hydrogenated at 10 Bar, in the presence of 10% palladium on charcoal (1.5g), at 20-25°C. The reaction was exothermic and required cooling. After *circa* 15 min hydrogen uptake ceased and the reaction was checked for completion by HPLC. The reaction mixture was filtered through celite, the pad washed clean with absolute ethanol (100 mL), and the title compound obtained after evaporation of the solvent as a thick oil (29.55 g, quantitative yield).

Method B

A solution of Intermediate 8 (30 g) in absolute ethanol (300 mL) was hydrogenated at 5 Bar, in the presence of (61% wet) 5% palladium on charcoal (1.5g), at 20-30°C. The reaction was exothermic and required cooling. After *circa* 35 min hydrogen uptake ceased and the reaction was checked for completion by HPLC. The reaction mixture was filtered through celite, the pad washed clean with absolute ethanol (100 mL), and the title

compound obtained after evaporation of the solvent as a thick oil (29.55 g, quantitative yield).

5 δ H (DMSO d_6) 8.32 (1H, d), 6.88 (2H, d), 6.48 (2H, d), 4.93 (2H, b,s), 4.30 (1H, s), 4.10 (2H, q), 4.02 (1H, m), 2.88 (2H, m), 1.4-1.75 (10H, b,m), 1.16 (3H, t). ESI⁺ ($m/z+1$) 343.3

INTERMEDIATE 10

3-(4-Nitrophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamino)propionic acid ethyl ester

10 4-Nitro-(L)-phenylalanine ethyl ester hydrochloride (28.6g) was suspended in dichloromethane (290 mL) to which a solution of potassium carbonate (8.0 g) in water (100 mL) was added slowly with stirring. After removal of the aqueous phase, the organic layer was washed with water (2 x 50 mL) and then dried (Na₂SO₄). Following removal of the drying agent, solid Intermediate 7 (16.1g)

15 was added portion-wise to the stirred dichloromethane solution. The resulting mixture was left to stir-out overnight at 20-25°C under nitrogen. The solution was sequentially washed with 5% aqueous sodium bicarbonate (100 mL), and water (2 x 50 mL), then dried (Na₂SO₄) prior to solvent removal *in vacuo* which afforded the title compound as an off-white foam (38.6g, 99.2% yield).

20 δ H (DMSO d_6) 8.78 (1H, d), 8.28 (2H, d), 7.66 (2H, d), 4.54 (1H, s), 4.52 (1H, m), 4.28 (2H, q), 3.84 (2H, dd), 3.72 (2H, q), 3.46 (1H, dd), 3.25 (1H, dd), 1.97 (2H, m), 1.38 (1H, d), 1.31 (1H, d), 1.28 (3H, t). ESI⁺ ($m/z+1$) 375.2.

INTERMEDIATE 11

3-(4-Aminophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamino)-propionic acid ethyl ester

25 A solution of Intermediate 10 (41.4 g) in ethanol (400 mL) was hydrogenated at 10 Bar in the presence of 5% palladium on charcoal (3.0 g) for 1 hour at 20-40°C. The catalyst was removed by filtration through celite at 40°C, under an

30 inert atmosphere, and the cake washed with fresh ethanol (2 x 50 mL). After removal of *circa* 300 ml of alcohol by vacuum distillation of the combined liquors at 40°C, the residual solution was allowed to cool whereupon the title compound crystallised out (off-white needles m.p. 157-159°C, 36.3g, 95.1%).

δ H (DMSO d_6) 8.5 (1H, d), 6.88 (2H, d), 6.49 (2H, d), 4.92 (2H, b,s), 4.38 (1H, s), 4.12 (2H, q), 4.07 (1H, m), 3.73 (2H, m), 3.58 (2H, m), 2.94 (1H, dd), 2.77 (1H, dd), 1.88 (2H, 2dd), 1.43 (1H, b,d), 1.31 (1H, b,d), 1.18 (3H, t).

5 **INTERMEDIATE 12**

2(S)-(2-Bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-3-(4-nitrophenyl)-propionic acid ethyl ester

Powdered N-bromosuccinimide (4.98g) was added portionwise to a stirred solution of the Intermediate 8 (10.3g) in ethyl acetate (100 mL) at 20-25°C over 90 minutes. After another 30 minutes, and following an LC completion check, the reaction was quenched by addition of sodium sulphite (0.5g) in water (50 mL). The organic phase was then washed with water (2 x 50 mL), dried ($MgSO_4$), filtered and evaporated to give the product as an off-white foam (12.4g, quantitative yield). 1H NMR (D_6 -DMSO) δ 0.95-1.84 (10H, m); 1.28 (3H, t); 3.14 (1H, dd); 3.38 (1H, dd); 4.19 (2H, q); 4.85 (1H, m); 7.64 (2H, d); 8.20 (2H, d); 8.98 (1H (b)d) ppm. Mass Spectrum: (ESI⁺) 451.1/453.1

INTERMEDIATE 13

3-(4-Amino-phenyl)-2(S)-(2-bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-propionic acid ethyl ester

Method A

Crude Intermediate 12 was re-dissolved in ethanol (100 mL) and the solution added to 50% wet, 5% palladium on charcoal (0.5g). The resulting preparation was hydrogenated at atmospheric pressure at 20-25°C until the theoretical volume of gas had been taken up and the reduction had been shown to be complete by LC. Following catalyst removal by filtration, the solvent was removed *in vacuo* to leave the product as an off-white foam (11.1g, 95.3%).

Method B

Intermediate 8 (10g) was dissolved in ethyl acetate (100 mL) and hydrogenated at 20-25°C, at atmospheric pressure, in the presence of 50% wet, 5% palladium on charcoal (0.5g). Once the reduction was complete, the catalyst was filtered off and powdered N-bromosuccinimide (NBS, 4.1g) added portion-wise to the liquors over 30 minutes. An in-process completion

check showed 80% conversion to product. Further NBS (1.0g) was added subsequently to consume all the starting material. The reaction was quenched with 1% sodium sulphite solution (50 mL), and the organic phase extracted with water (2 x 50 mL). The solid that precipitated during the last water wash was collected by filtration and dried *in vacuo* at 60°C to afford the title compound (8.7g, 74.9% yield, LC 98% PAR). Further product (1.22g), along with the dibromo- and tribromo-analogues (0.72g & 0.12g respectively) were isolated after chromatography of the mother liquors (silica gel; 2-5% MeOH in DCM).

¹H NMR (D₆-DMSO): δ1.02-1.88 (10H, m); 1.28 (3h, t); 2.89 (1H, dd); 3.08 (1h, dd); 4.20 (2H, q); 4.71 (1H, m); 5.01 (2H, (b)s); 6.53 (2H, d); 6.94 (2H, d); 8.94 (1H, (b)d) ppm. Mass Spectrum: (ESI⁺) 421.1/423.1

INTERMEDIATE 14

4-Nitro-(S)-Phenylalanine Hydroxyethyl ester Hydrochloride

Dry hydrogen chloride (68.3 g) was dissolved in ethylene glycol (994 mL) at <20°C and then solid 4-nitro-(S)-phenylalanine (198.7g) added with stirring. The mixture was heated to 80-85°C and held at this temperature for 2 h. After a LC completion check, the preparation was allowed to drift to 60°C and seeded with authentic product. Once crystallisation had initiated, the resulting suspension was cooled further to 20°C and stirred out overnight. The 4-nitro-(S)-phenylalanine hydroxyethyl ester hydrochloride was collected by filtration, washed *in situ* with dimethoxyethane (795 mL), and then dried *in vacuo* at 40-45°C to constant weight (white powder m.p. 195-197°C, 187.0g, 73.9% yield). ¹H NMR (D₆-DMSO): δ3.27 (2H, ddd); 3.42 (2H, m); 4.01 (2H, m); 4.27 (1H, t); 4.88 (1H, b,s); 7.52 (2H, d); 8.11 (2H, d); 8.76 (3H, b,s) ppm. Mass Spectrum: ESI⁺ (*m/z*+1) 255.0

INTERMEDIATE 15

3-(4-Nitrophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamin)propionic acid hydroxy ethyl ester

Solid spiro[3,5]nonane-1,3-dione (70.0 g) was charged to a stirred suspension of Intermediate 14 (120.0 g) in ethyl acetate (1200 mL) containing triethylamine (64 mL) at 20-25°C. The whole was then boiled under reflux for 2 h and checked for completion (LC). Having established that the reaction had finished, the preparation was cooled to 20°C and water (360 mL) added. 2M Hydrochloric acid (46 mL) was added subsequently to adjust the pH from 6 to 1.5. After removal of the aqueous phase, the organic layer was washed successively with 10% brine (330 mL), 5% sodium carbonate solution (250 mL), and 10% brine (2 x 330 mL), prior to being dried with magnesium sulphate. The solution was evaporated to dryness *in vacuo* to obtain the title compound as a clear, orange-brown gum (yield by LC assay 160.5g, 94.1%). This intermediate was used directly in the next step. ¹H NMR (D₆-DMSO): δ1.07-1.70 (10H, b,m); 3.16 (1H, dd); 3.37 (1H, dd); 3.59 (2H, m); 4.14 (2H, t); 4.38 (1H,m); 4.40 (1H, s); 4.88 (1H, t); 7.46 (2H, d); 8.19 (2H, d); 8.38 (1H, d) ppm. Mass Spectrum: ESI⁺ (*m/z*+1) 389

INTERMEDIATE 16

3-(4-Aminophenyl)-2(S)-(3-oxo-7-oxaspiro[3.5]non-1-en-1-ylamino)-propionic acid hydroxyethyl ester

Intermediate 15 (68.5 g) in ethyl acetate (350 mL) was hydrogenated at 5 Bar and <30°C in the presence of 5% palladium on charcoal (61% wet) (3.4 g), until gas uptake ceased (*circa* 1 h). After filtering off the catalyst and washing the pad with ethyl acetate (2 x 100 mL), the combined organic solutions were evaporated to dryness *in vacuo* to furnish the title compound as a straw coloured foam, in essentially quantitative yield (63.2 g). ¹H NMR (D₆-DMSO): δ1.08-1.79 (10H, b,m); 2.88 (1H, dd); 3.04 (1H, dd); 3.64 (2H m); 4.11 (1H, m); 4.18 (2H, m); 4.39 (1H, s); 4.89 (1H, t); 4.99 (1H, b,s); 6.53 (2h, d); 6.96 (2H, d); 8.33 (1H, d) ppm. Mass Spectrum: ESI⁺ (*m/z*+1) 359.1

EXAMPLE 1

Ethyl 2(S)-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amin]ph nyl}propanoat

A solution of Intermediate 2 (3.1g) in dichloromethane (DCM, 5 mL) was added dropwise to N-methyl morpholine (1.6g) and Intermediate 9 (4.64g) dissolved in DCM (40 mL) at 0-5°C. After stirring for 1 h, the organic phase was washed successively with 2M hydrochloric acid (10 mL), 10% sodium bicarbonate (10 mL) and saturated brine (10 mL), then dried (MgSO₄) and evaporated *in vacuo*, to leave a pale yellow powder (6.72 g). The crude product was purified by a hot reslurry in 2:1 ethyl acetate: methyl t-butyl ether (60 mL). The suspension was cooled, filtered, and the solid washed with 1:2 ethyl acetate: methyl t-butyl ether (2 x 30 mL). Dry title compound was obtained after drying *in vacuo* (5.26 g, 72.4% yield, m.p. 194°C). ¹H (CDCl₃, 300K) 10.86 (1H, s), 8.78 (2H, s), 8.34 (1H, d, *J* 8.5Hz), 7.56 (2H, d, *J* 8.5Hz), 7.25 (2H, d, *J* 8.5Hz), 4.36 (1H, s), 4.20-4.11 (3H, m), 3.13 (1H, dd, *J* 13.8, 5.3Hz), 3.00 (1H, dd, *J* 9.2, 13.8Hz), 1.67-1.19 (10H, m), 1.17 (3H, t, *J* 4.1Hz); *m/z* (ES⁺, 70V) 516.0 and 518.0 (MH⁺).

EXAMPLE 2

Ethyl 2(S)-[(2-bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate

A solution containing Example 1 (500mg, 0.97mmol) and triethylamine (2eq, 270μl) in THF (10ml) at 0° was treated dropwise with a solution of bromine (1.1eq, 170mg) in THF (5ml). After 20mins the reaction was allowed to warm to room temperature prior to dilution with EtOAc (100ml). The crude reaction mixture was washed with saturated aqueous NaHCO₃ (20ml) and brine (20ml), dried (MgSO₄) filtered and concentrated *in vacuo*. The residual foam was chromatographed (SiO₂; EtOAc) to give the title compound as a white powder (511mg, 0.86mmol, 95%). ¹H (CDCl₃, 300K) 8.48 (2H, s), 8.05 (1H, s br), 7.52 (2H, d *J* 8.4Hz), 7.04 (2H, d *J* 8.5Hz), 5.81 (1H, d br, *J* 8.3Hz), 4.98-4.91 (1H, m), 4.21 (2H, q, *J* 7.1Hz), 3.21 (2H, d *J* 5.3Hz), 1.70-1.66 (4H, m), 1.53-1.44 (4H, m), 1.28 (3H, t *J* 7.1Hz), 1.20-1.16 (2H, m); *m/z* (ES⁺, 70V) 597.9 and 595.0 (MH⁺).

EXAMPLE 3

2(S)-[(2-Bromo-3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 2 (511mg, 0.86mmol) in THF (5ml) was treated in a single portion with LiOH.H₂O (50mg, 1.19mmol) in H₂O (1ml) and the reaction stirred at room temperature for 2h. The reaction was then quenched by the addition of HOAc (glacial, 1ml) and the volatiles removed *in vacuo*. Water (10ml) was then added to the residue to effect precipitation. The precipitate was collected by vacuum filtration and the residue washed with water (2 x 5ml). Drying under vacuum gave the title compound as a fine white solid (421mg, 0.74mmol, 87%). ¹H (DMSO d₆, 390K) 10.34 (1H, s), 8.67 (2H, s), 7.53 (2H, s br), 7.26 (2H, d Δ 8.26Hz), 4.67 (1H, m), 3.26-3.22 (1H, m), 3.13-3.08 (1H, m), 1.67-1.21 (10H, m); m/z (ES⁺, 70V) 569.9 and 567.9 (MH⁺).

EXAMPLE 4

Hydroxyethyl 2(S)-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Intermediate 2 (31.0 g) was introduced dropwise to a well-stirred solution of Intermediate 16 (50.0 g) in ethyl acetate (500 mL) and triethylamine (25 mL). The reaction temperature was kept below 25°C throughout by external cooling. Acylation of the starting material was complete after a 1.5 hour stir-out. Water (150 mL) was charged at the end of this period, followed by sufficient 2M hydrochloric acid to lower the pH to 1 – 1.5. Following separation, the organic phase was washed with water (2 x 150 mL), 5% sodium carbonate solution (150 mL) and 10% brine (2 x 150 mL) then dried (MgSO₄), filtered and evaporated *in vacuo* to afford the title compound as a yellow-brown foam (71.1g, 95.6% yield). ¹H NMR D₆-DMSO: δ 1.1-1.73 (10H, b,m); 2.98 (1H, dd); 3.20 (1H, dd); 3.64 (2H, m); 4.13 (2H, t); 4.24 (1H, m); 4.39 (1H, s); 4.87 (1H, t); 7.28 (2H, d); 7.59 (2H, d); 8.37 (1H, d); 8.81 (2H, s); 10.88 (1H, s) ppm. Mass Spectrum: ESI⁺ m/z 532/534

EXAMPLE 5

2-Hydroxy thyl 2(S)-(2-bromo-3-oxo-spiro[3.5]non-1- n-1-ylamin)-3-(4-[(3,5-dichloroisonicotinoyl)amin]ph nyl}propan at

Method A

To a solution of the compound of Example 3 (0.5g, 0.89mmol) in DMF (2ml) was added EDC (190mg, 0.97mmol), HOBT (140mg, 1.03mmol) and ethylene glycol (2.5ml). The mixture was stirred at room temperature for 48h then partitioned between EtOAc (15ml) and water (10ml). The aqueous layer was separated and the organics washed with water (3 x 5ml), brine (10ml), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a crude solid. The crude was chromatographed (SiO₂; EtOAc) to give the title compound as a white powder (287mg, 53%). ¹H (300MHz, DMSO d⁶) 8.88 (1H, d, J 9.2Hz), 8.79 (2H, s), 7.59 (1H, d, J 8.5Hz), 7.26 (2H, d, J 8.5Hz), 4.86 (1H, m), 3.62 (1H, m), 3.25 (1H, dd, J 14.0, 4.6Hz), 3.04 (1H, dd, J 14.0, 9.4Hz), 1.58-1.79 (6H, m), 1.37 (1H, d, J 12.7Hz), 1.11 (2H, br).

Method B

Powdered N-bromosuccinimide (19.3 g) was added portionwise to a solution of Example 4 (60.7 g) in ethyl acetate (610 mL) at 0-5°C over 2 h. LC monitoring was used to check reaction progress and suppress over-bromination of the starting material. Upon completion, the reaction was quenched with a solution of sodium sulphite (3.0 g) in water (60 mL). The organic phase was washed with water (2 x 100 mL), and then concentrated to give a 25% w/v solution of the product, with concomitant azeo-drying, by distillation at atmospheric pressure. The product began to crystallise out towards the end of the step. After cooling to 20°C over 2 h, and stirring overnight, the resulting suspension was filtered and the solid washed with cold (0-5°C) ethyl acetate (2 x 80 mL). The title compound was thus obtained as a fawn microcrystalline powder after drying to constant weight at 70°C *in vacuo* (m.p. 210-212°C, 63.2 g, 90.6% yield). ¹H NMR D₆-DMSO: δ1.05-1.78 (10H, b,m); 3.04 (1H, dd); 3.25 (1H, dd); 3.66 (2H, m); 4.19 (2H, t); 4.84 (1H, m); 4.90 (1H, t); 7.28 (2H, d); 7.59 (2H, d); 8.80 (2H, s); 8.92 (1H, d); 10.92 (1H, s) ppm. Mass Spectrum: ESI⁺ (*m/z*+1) 612.0

EXAMPLE 6a

Ethyl-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]-2(S)-(3-oxo-spiro[3.5]non-1-en-1-ylamino)propanoate, di-(4-toluoyl)-2(R), 3(R)-tartaric acid salt

Intermediate 5 (35.6 g) was charged to a solution of Intermediate 9 (81.6 g) in absolute ethanol (727 mL). Ethanolic hydrogen chloride, prepared in a preliminary step by adding acetyl chloride (1.5 mL) dropwise to chilled ethanol (89 mL), was then introduced, and the resulting mixture heated to 40°C for 16 h under nitrogen. The reaction was quenched with triethylamine (36 mL) and then solvent swapped to solution in ethyl acetate (820 mL) by distillation at atmospheric pressure. After cooling to ambient temperature, the ester solution was washed with 15% brine (3 x 400 mL) prior to azeo-drying. Whilst at reflux, a solution of di-(4-toluoyl)-2(R), 3(R)-tartaric acid (92.1 g) in ethyl acetate (440 mL) was added, the preparation brought off the boil, seeded, and then cooled to 20°C over 12 h. The title compound was filtered off, washed with ethyl acetate (2 x 220 mL), and subsequently dried *in vacuo* at 45°C to give granular yellow solid (156.2 g, 76.5% yield). ¹H NMR (D₆-DMSO): δ 1.22 (1H, m); 1.28 (3H, t); 1.47-1.84 (9H, b,m); 2.48 (6H, s); 3.07 (1H, dd); 3.24 (1H, dd); 4.26 (2H, q); 4.28 (1H, m); 4.45 (1H, s); 5.92 (2H, s); 7.22 (1H, d); 7.31 (2H, d); 7.50 (4H, d); 7.78 (1H, d); 7.87 (2H, d); 7.99 (4H, d); 8.28 (1H, d); 8.51 (1H, d); 8.76 (1H, d); 9.64 (1H, b,s); 9.93 (1H, s) ppm

Example 6b

Ethyl-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]-2(S)-(3-oxo-spiro[3.5]non-1-en-1-ylamino)propanoate, oxalate salt

A solution of Intermediate 8 (20.0 g) in ethanol (80 ml) was hydrogenated over 5 % w/w Pd/C, ca. 50 % wet (2.5 % w/w dry) at ca. 50 psi until hydrogen uptake ceased. The mixture was filtered, washing with ethanol (60 ml). To this solution was added Intermediate 5 (8.04 g) and a solution of acetyl chloride (0.383 g) in ethanol (15 ml) and the mixture heated at 60°C for 3.5 h. The solution was cooled to 20°C and triethylamine (5.93 g) added. The turbid solution was then filtered, washing with ethanol (10 ml) and a solution of oxalic acid (4.62 g) in ethanol (15 ml) added followed by seeds of Intermediate 5 oxalate salt. When crystallisation was complete the mixture was filtered,

washing with ethanol (20 ml) to give the title compound as a yellow solid, 14.7 g, 53.6 %. C: 63.72 %, H: 5.71 %, N: 9.88 %, C₃₀H₃₂N₄O₇ requires C: 64.26 %, H: 5.76 %, N: 10.00 %. ¹H NMR, DMSO-d₆ : δ 1.2 (3H, t), 1.4 – 1.7 (10H, m), 3.0 (1H, dd), 3.15 (1H, dd), 3.9 – 4.9 (2H, broad), 4.15 (3H, m), 4.35 (1H, s), 7.10 (1H, d), 7.20 (2H, d), 7.70 (1H, d), 7.75 (2H, d), 8.15 (1H, d), 8.40 (1H, d), 8.65 (1H, d), 9.5 – 9.8 (1H, broad), 9.95 (1H, s).

EXAMPLE 7

Ethyl-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]-2(S)-(3-oxo-spiro[3.5]non-1-en-1-ylamino)propanoate

Intermediate 5 (24.3 g) and Intermediate 9 (45.8g) were suspended in ethanol (300 mL) and heated to 60°C for 4 h, under nitrogen. Ethanol was removed *in vacuo* and the residue taken up in ethyl acetate (350 mL). The latter solution was washed carefully with a solution of potassium carbonate (10.4g) in water (100 mL), followed by saturated brine (100 mL). The ethyl acetate solution was evaporated to dryness under vacuum, and the residue purified by column chromatography on silica, eluting with 10% ethanol in ethyl acetate, to give the title compound as an orange-yellow foam (56.9g, 90.4% yield). δH (CDCl₃) 9.61 (1H, s), 8.65 (1H, d, J 5.7Hz), 8.25 (1H, d, J 5.8Hz), 7.71 (2H, d, J 8.4Hz), 7.63 (1H, d, J 8.5Hz), 7.12 (2H, d, J 8.5Hz), 7.05 (1H, d, J 5.8Hz), 5.80 (1H, m), 4.55 (1H, s), 4.29 (2H, q, J 7.2Hz), 3.13 (2H, m), 1.87–1.25 (14H, m); *m/z* (ES⁺, 70V) 471.1 (MH⁺).

EXAMPLE 8

Ethyl 2(S)-(2-bromo-3-oxo-spiro[3.5]non-1-en-1-ylamino)-3-[4-([2,7]naphthyridin-1-ylamino)phenyl]propanoate

Method A

A stirred solution of the compound of Example 7 (300mg, 0.637mmol) and triethylamine (1.2eq, 100μl) in THF (10ml) at 0° was treated dropwise with a solution of bromine in DCM (2% v/v, 2.1ml, 1.2eq). After 12h the reaction was diluted with DCM (50ml) and washed successively with saturated aqueous NaHCO₃, dried (MgSO₄) filtered and concentrated *in vacuo*. The residual foam was triturated with diisopropylether and the resulting solid collected and

dried *in vacuo* to give the title compound as a pale yellow powder (0.45mmol, 76%).

Method B

A suspension of Example 6a (250 g) in ethyl acetate (1500 mL) was stirred
5 with 10% aqueous potassium carbonate (545 mL) to give an organic solution
of Example 7. The latter was washed with water (250 mL) and 15% brine (250
mL) then cooled to -10°C in the reaction vessel. N-Bromosuccinimide (51.4 g)
was added portionwise to the solution over 1 h at -10 to -5°C . Once all the
reagent had been charged, the preparation was warmed to 40°C over 1 h
10 then kept at this temperature for another 2 h. Reaction progress was closely
monitored by HPLC. As soon as Example 7 had all been consumed, the
halogenation was quenched with 2% aqueous sodium sulphite (200 mL). The
organic phase was washed with water (250 mL) and saturated brine (250 mL)
prior to a polish filtration. Wet ethyl acetate was then distilled out to leave a
15 dry 25% w/v solution of the product. The concentrate was seeded just below
boiling, and diluted slowly with n-heptane (963 mL), once crystal growth had
become apparent. Further crystallisation occurred during cooling to 20°C over
4 h. Filtration of the resulting slurry afforded the title compound which was
washed with 2:1 heptane: ethyl acetate (150 mL) and heptane (150 mL)
20 before being dried *in vacuo* at $40-45^{\circ}\text{C}$ (m.p. $192.5-195^{\circ}\text{C}$, 147.8g, 92.3%).

Method C

Intermediate 13 (14.4 g), Intermediate 5 (6.47 g) and absolute ethanol (140
mL) were heated to $40-45^{\circ}\text{C}$ and stirred out under nitrogen. LC monitoring
showed the reaction to be complete after 12 h, whereupon triethylamine (10
25 mL) was added and the mixture stirred for 0.5 h. After removal of solvent *in*
vacuo ($40-50^{\circ}\text{C}/50-100$ mBar), the residual orange-red paste (31.1g) was
partitioned between ethyl acetate (150 mL) and water (100 mL). The aqueous
phase was back-extracted with ethyl acetate (50 mL) and then the combined
organic layers were distilled at atmospheric pressure to leave 3 volumes
30 solvent with respect to the theoretical yield of product. The concentrated
solution was seeded at 75°C and then heptane (140 mL) added *via* a syringe
pump over 2 h, whilst maintaining this temperature. With most of the product
crystallised, the mixture was cooled to 20°C and held for 1 h prior to filtration.
Following heptane washes (2 x 50 mL) and drying at 60°C to constant weight,

the crude product was obtained as a pale orange solid [17.9g, 95.1% yield; LC 93.8% PAR, 91.2%w/w assay (*versus* an analytical specimen) => 86.7% active ingredient yield].

5 δ H (CDCl₃) 9.81 (1H, s), 8.64 (1H, d, \underline{J} 5.7Hz), 8.29 (1H, d, \underline{J} 5.8Hz), 7.75 (2H, d, \underline{J} 8.3Hz), 7.60 (1H, d, \underline{J} 5.8Hz), 7.12 (2H, d, \underline{J} 8.4Hz), 7.08 (1H, d, \underline{J} 5.7Hz), 5.91 (1H, m), 5.03 (1H, m), 4.28 (2H, q, \underline{J} 7.1Hz), 3.29 (2H, m), 1.81–1.39 (10H, m), 1.35 (3H, t, \underline{J} 7.1Hz); *m/z* (ES⁺, 70V) 550.0 (MH⁺).

10 **EXAMPLE 9**

Ethyl 3-[4-([2,7]naphthyridin-1-ylamino)phenyl]-2(S)-[(3-oxo-7-oxa-spiro[3.5]non-1-en-1-yl)amino] propanoate

Acetyl chloride (1 mL) was added cautiously to stirred ethanol (50 mL) with exclusion of moisture. This solution was then added to a stirred suspension of
15 the Intermediate 11 (24.0 g) and Intermediate 5 (12.0 g) in ethanol (200 mL) and the whole heated to 60°C under nitrogen for 2 h. Ethanol was removed *in vacuo* and the residue taken up in ethyl acetate (300 mL). The latter solution was washed with 5% sodium hydroxide solution (100 mL) followed by water (2 x 50 mL). Some tarry material was cut away with the aqueous phases. The
20 organic phase was dried (Na₂SO₄) and its volume reduced to approximately 100 mL, crystallisation of the product occurred after seeding. After stirring out at 0-5°C for 1 h the title compound was isolated and dried at 50°C *in vacuo* (28.2 g, pale yellow solid m.p. 112°C, 85.6% yield). δ H (DMSO d₆) 10.02 (1H, s), 9.73 (1H, s), 8.78 (1H, d), 8.33 (1H, d), 7.98 (2H, d), 7.89 (1H, d), 7.44
25 (2H, d), 7.32 (1H, d), 4.61 (1H, s), 4.42 (1H, m), 4.36 (2H, q), 3.94 (2H, m), 3.80 (2H, m), 3.34 (1H, dd), 3.17 (1H, dd), 2.11 (2H, m), 1.69 (1H, d), 1.58 (1H, d), 1.40 (3H, t). ESI⁺ (*m/z*+1) 473.3

EXAMPLE 10

30 **Ethyl 2(S)-[(2-isopropylsulfanyl-3-oxo-7-oxa-spiro[3.5]non-1-en-1-yl)amino]-3-[4-([2,7]naphthyridin-1-ylamin)phenyl]propanoat**

Sulphuryl chloride (13.6 g) was added drop-wise to diisopropyl disulphide (25.0 g) in tetrahydrofuran (THF, 150 mL) at 0-5°C under nitrogen. After

stirring out for 30 minutes, the resulting isopropyl sulphenyl chloride preparation was introduced slowly, from a graduated dropping funnel, to a solution of Example 9 (30.0 g) in THF (500 mL), held at the same temperature. Conversion to product was complete after 85 mL of the stock solution had been charged. The reaction was quenched with 10% sodium bicarbonate solution (175 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic solutions then washed with saturated brine (100 mL). The isolated organic phase was solvent swapped to ethanol (650 mL), by distillation at atmospheric pressure, from which the product crystallised on cooling. This suspension was filtered at 20°C and the title compound washed with ethanol (2 x 30 mL) prior to drying *in vacuo* at 50-60°C (26.9g; 77.5% yield, off-white powder m.p. 221°C). δ H (DMSO d_6 , 390K) 9.83 (1H, s), 9.52 (1H, s), 8.94 (1H, d, \underline{J} 9.5Hz), 8.65 (1H, d, \underline{J} 5.6Hz), 8.15 (1H, d, \underline{J} 5.7Hz), 7.78 (2H, d, \underline{J} 8.5Hz), 7.68 (1H, d, \underline{J} 5.6Hz), 7.23 (2H, d, \underline{J} 8.5Hz), 7.12 (1H, d, \underline{J} 5.7Hz), 5.26 (1H, m), 4.19 (2H, q, \underline{J} 7.1Hz), 3.81-3.76 (2H, m), 3.64-3.55 (2H, m), 3.20 (1H, dd, \underline{J} 13.8, 4.3Hz), 2.96 (1H, dd, \underline{J} 13.8, 10.3Hz), 2.81-2.74 (1H, m), 2.06-1.93 (2H, m), 1.50-1.47 (1H, m), 1.32-1.28 (1H, m), 1.23 (3H, t, \underline{J} 7.1Hz), 1.07 (3H, d, \underline{J} 6.6Hz), 1.05 (3H, d, \underline{J} 6.6Hz); m/z (ES⁺, 70V) 547.2 (MH⁺).